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SPONTANEOUS PERFORATION OF THE ESOPHAGUS

Report of Three Cases Successfully Treated Surgically

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BOSTON

SPONTANEOUS perforation of the presumably normal esophagus has been considered a rare lesion. A recent increase in the number of reports on this subject indicates that it may not be as unusual as was formerly believed. Barrett,[1] Olsen and Clagett[2] and Kinsella[3] have recently considered this subject so completely that further review is unnecessary. The original, classic description of the lesion by Boerhaave in 1723 and the first diagnosis made during life by Walker[4] in 1914 represent historical milestones. In modern times, the diagnosis has been made before death a number of times, but seldom early enough to permit treatment. Recent advances in thoracic surgery, as well as the development of the antibiotics, have made it possible to treat such patients successfully when the diagnosis is made early. Therefore, an awareness of this lesion and its characteristic symptomatology becomes increasingly important.

Spontaneous perforation differs from other types of perforation of the esophagus. In traumatic perforations the history of aspiration of a foreign body or a previous operative manipulation serve to focus attention on the esophagus. Occasionally, a peptic ulcer of the esophagus perforates and the history is similar to that of patients with spontaneous perforation. However, the history of previous symptoms of ulcer should make one suspicious of the underlying cause. Since the pre-existing ulcer usually sets up a reaction in the mediastinum, perforation is generally directly into the pleural cavity, with the formation of a hydropneumothorax, an infrequent occurrence in spontaneous perforation of the esophagus.

In most of the cases of spontaneous perforation of the esophagus described in the literature, there has been no background in the history that would lead one to suspect disease of the esophagus. Furthermore, since most cases occur during vomiting, there is immediate flooding of the mediastinum with the highly irritant gastric contents. This gives rise to the characteristic symptoms usually noted, which are seldom present when the perforation is traumatic.

Commonly, the history is one of a patient vomiting for one of many reasons — most frequently after a bout of alcohol ingestion. In the course of vomiting, and usually after severe retching, there has been sudden severe pain, usually referred to the precordium or epigastrium or both. This pain is generally associated with a shock reaction, dyspnea and, at times, cyanosis. The physician first seeing the patient frequently considers coronary thrombosis the most likely diagnosis although including the possibility of a perforated gastric ulcer. The blood pressure is low, the pulse is rapid, the temperature is subnormal, and there may be upper abdominal tenderness and spasm. These signs usually continue for the first few hours after onset. The blood pressure gradually rises but generally remains at a lower than normal level. The temperature rises, and signs of a pleural effusion develop. This occurs almost always on the left but has occasionally developed on the right. Within six to twelve hours of onset, air may be palpable in the neck, and this, with the previous history, is diagnostic of perforation of the esophagus. From the history, one should always suspect the condition in any patient who has sudden severe epigastric or precordial pain that comes on during vomiting.

Since most patients are hospitalized almost immediately because of the severe nature of their illness, and since perforated ulcer is suspected, it is usual to have an x-ray examination of the abdomen in a search for subphrenic air. Such a procedure can be most helpful in the diagnosis, since air behind the heart is frequently seen and is one of the most characteristic findings. Even in the early stages, a small pleural effusion has been noted. The usual chest x-ray film at this time may also show air in the upper mediastinum. Under the circumstances here described, such a finding is diagnostic.

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Untreated, the course is progressively downhill, and the majority of patients have died within forty-eight hours of the onset of the lesion.[1] There are described in the literature 2 cases in which a localized empyema or mediastinal abscess developed, the perforation of the esophagus closed spontaneously, and recovery followed drainage of the empyema or mediastinal abscess.[6] Such a localization must be rare, the usual outcome of esophageal perforation being one of diffuse mediastinal infection that is rapidly fatal. Attempts to drain the local infection by mediastinotomy or pleural drainage during the acute stage have generally been unsuccessful.[1, 6]

Moore and Murphy[7] have recently reported an unusual case treated conservatively. After walling off had occurred, thoracotomy repair was successful. These authors suggest the use of the conservative measures of pleural drainage and jejunostomy, believing that, in many cases, the perforation will heal spontaneously. In the cases in which healing does not occur, operative intervention can be undertaken.

There are certain similarities in the development of this lesion to that of perforated peptic ulcer, and in a general way, one believes that correction of this defect should follow the same lines as the treatment of perforated peptic ulcer. It appears necessary that adequate drainage of the mediastinum, with closure of the perforation, be provided. Ideally, this is accomplished by thoracotomy, wide opening of the mediastinal pleura, closure of the esophageal defect, re-expansion of the lung and closure of the chest, with intercostal tube drainage. Attempts at such a procedure have been made by various surgeons. Collis[8] and Foggitt[9] completed their operations successfully, but the patients died a few hours later. Kinsella's[2] patient was well on the road to recovery, only to die of a pulmonary embolism on the ninth postoperative day. More recently, Barrett[10] and Olsen and Claggett[3] have treated patients definitively with success.

The decision to undertake operation for such patients is not simple. These patients are acutely ill; their blood pressure is extremely low, and they are poor candidates for anesthesia. However, since the results without surgical repair are so disastrous, operation is justified despite the patient's condition at the time the patient is first seen. Obviously one first prepares the patient, as necessary, by thoracentesis, gastric suction and transfusions. However, delay longer than a few hours will permit further deterioration of the patient's condition.[6] One can be encouraged by the fact that immediately after opening of the mediastinal pleura, the patient should be considerably improved by relief of mechanical compression of mediastinal structures. In Case 2 reported below, the blood pressure remained at shock levels until the chest cavity was entered and the mediastinal pleura opened, the tension within the mediastinum thus being relieved. From that time, the patient's blood pressure remained normal throughout the operation. This same sequence of events was also true in Barrett's[10] successfully treated case.

Case Reports

Case 1. H. M., a 45-year-old man, was admitted to the Mount Auburn Hospital on July 11, 1947, because of severe pain in the upper abdomen and lower chest. The patient had always been well until 3 months prior to admission, when he began to have dizzy spells, for which his physician was unable to find a cause. On the night of July 11, the patient felt nauseated and vomited. Because the feeling of nausea persisted, he attempted to make himself vomit. During one of these attempts, there was a sudden onset of severe pain in the left anterior portion of the chest and upper abdomen. The pain was unbearable from its onset, and a physician was called immediately. When seen, the patient was in shock; the temperature was subnormal, and the pulse 110. He was immediately sent to the hospital with a tentative diagnosis of coronary thrombosis.

At the time of admission, electrocardiogram and x-ray films of the abdomen were normal. A chest plate at that time (Fig. 1) showed a slight amount of fluid at the left base.

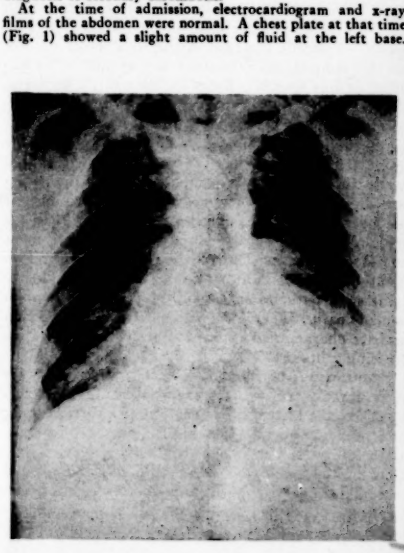

Figure 1. *Posteroanterior Roentgenograms of the Chest on Admission in Case 1, Showing a Small Amount of Fluid at the Left Base.*

Twenty-four hours after admission, x-ray study revealed a pleural effusion filling the left side of the chest (Fig. 2). At that time the blood pressure was normal; the temperature was 100°F., and the pulse 110, and he was relatively comfortable. During the next 24 hours, the patient's condition deteriorated gradually, and a thoracic surgeon was consulted.

Physical examination at that time showed that the trachea was deviated to the right. There was subcutaneous emphysema in the right supraclavicular fossa. The entire left side of the chest was flat to percussion, and the breath sounds were absent. The abdomen was voluntarily spastic, without tenderness or palpable masses.

A diagnosis of spontaneous perforation of the esophagus, with rupture of the mediastinal abscess into the pleural cavity, was made. Review of the previous x-ray films showed air present in the mediastinum (Fig. 2).

Thoracentesis was performed immediately, and 500 cc. of seropurulent fluid was removed. Direct smear showed gram-positive cocci, culture of which later proved to be pneumococci. Because of the patient's poor condition and the fact that the lesion had been present for approximately 60 hours, radical operation was not considered. Intercostal drainage was accomplished, 1500 cc. of purulent fluid being removed, after which the breath sounds were well heard throughout the left side of the chest. Penicillin and streptomycin were given in large doses. On the following day, the patient's condition was satisfactory; the tube was functioning well. There appeared to be atelectasis of the left lung, and endotracheal suction was performed, with immediate expansion of the lung. Constant gastric suction was instituted, and the patient was

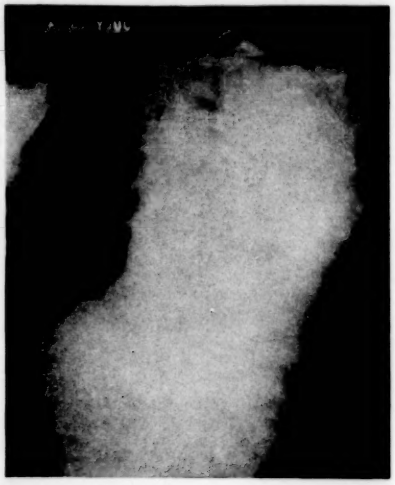

FIGURE 2. *Posteroanterior Roentgenogram of the Chest Twenty-Four Hours after Admission in Case 1.*

The left side of the chest is filled with fluid, and air can be seen in the upper mediastinum and neck.

maintained on intravenous administration of fluids and transfusions.

One week after admission, the patient's condition remained satisfactory, and a swallow of radio-opaque oil was given. This showed a definite perforation at the lower end of the esophagus, with the oil in the mediastinum and communicating with the pleural cavity.

On July 22 a rib-section drainage of the empyema was performed, and through the empyema cavity, a large mediastinal abscess was opened into the pleural cavity. Subsequently, the patient's condition appeared to become worse. There was considerable mobility of the underlying lung, and toxicity seemed to increase greatly. There was frequent regurgitation of gastric contents through the perforation into the empyema cavity. Such an incident usually coincided with a marked elevation of temperature. This was controlled by gastric suction. A jejunostomy was performed for feeding.

Four attempts to repair the linear laceration of the esophagus, which was easily seen at the bottom of the empyema cavity, were made at intervals of 10 to 14 days, without success in spite of what appeared to be a completely adequate three-layer closure of the esophagus. The patient's condition gradually improved, and after these failures, no further attempts to close the esophagus were made. The patient was allowed up and about, and gradually, over a period of 1 month after the last attempt at closure, the laceration in the esophagus closed and he was able to take food by mouth.

He was discharged home on November 4, 1947, with a jejunostomy tube in place, the empyema cavity widely opened, and moderate amounts of food being taken by mouth. The patient's condition gradually improved at home. The empyema wound closed. The jejunostomy tube was withdrawn, and approximately 1 year after the original perforation, he was eating normally and was working full time. Operative closure of a persistent jejunostomy fistula was necessary 1½ years after the original episode.

Because the perforation had existed sixty hours before diagnosis, it did not appear that the patient's condition would allow a major surgical procedure at that time. Therefore, temporary drainage of the pleural cavity was performed with an intercostal tube, and, later, wide-open drainage of the mediastinal abscess and empyema accomplished. For approximately three months, this patient was extremely ill — at times, even moribund. Repeated transfusions were necessary; he presented a problem of hydration and nutrition at all times. He lost a considerable amount of weight during the first two months, despite jejunostomy. Eventually, adequate feedings could be accomplished, and the weight was regained.

Bacteriologically, the only organism cultured from the mediastinal abscess or pleural fluid was a pneumococcus. The fact that this was the only organism present may have contributed to his ability to withstand the infection.

Attempts to close the esophagus within the empyema cavity, despite adequate technical closure, were completely unsuccessful, since the suture line was bathed in the empyema pus and sloughing occurred within forty-eight hours of the time of repair. Yet the patient's condition was never such that one would consider decortication of the empyema, closure of the esophagus, re-expansion of the lung and closure of the chest wall. All these procedures would have been necessary to produce definitive operative closure after the first month. Awaiting natural closure provided a successful, if long delayed, cure.

CASE 2. J. R., a 56-year-old man, was admitted to St. Elizabeth's Hospital on April 26, 1948, because of pain in the epigastrium and lower chest. For 2 days prior to admission, he had vomited intermittently without other symptoms. At 4:30 a.m. on the day of admission, he was suddenly awakened by nausea and vomiting. He vomited for approximately ½ hour, retching severely with the vomiting. Suddenly, during an attack of vomiting, he was seized with severe, excruciating pain in the lower chest and upper abdomen. At that time, examination of the chest and abdomen by his physician was negative. The patient was in moderate shock; the pulse was rapid, and it was the examining physician's impression that the patient had a penetrating ulcer. Morphine was ordered, and the patient was told to remain at rest. A few hours later, because the pain persisted, he was hospitalized.

Physical examination showed the patient to be in severe shock and obviously toxic. There was slight cyanosis of the face and neck. There was marked venous distention of the neck and arms, with some crepitation in the right supraclavicular area. Examination of the chest was essentially negative except for diminished breath sounds at the left base. The abdomen showed slight tenderness and spasm.

X-ray examination of the chest and upper abdomen revealed air in the mediastinum (Fig. 3 and 4), and the diagnosis of spontaneous rupture of the esophagus was made.

Operation was performed approximately 30 hours after the onset of pain. Under endotracheal nitrous oxide, oxygen and ether anesthesia, the blood pressure was 70/40. The pulse was of good quality and rapid, and the respirations were shallow. In the right lateral decubitus position, a 25-cm. oblique incision was made over the ninth rib, and very slight bleeding was encountered. A 25-cm. segment of the rib was removed, and the pleura was opened. The pleura was grossly discolored, appearing edematous and alternately black and gray. There were thick, black fibrin clots over the pleural surface, and there was a moderate amount of thin, gray, dirty, odorless fluid within the pleural cavity. The lung, which was loosely adherent to the diaphragm, was freed. The mediastinal pleura was bulging, and when it was opened, there was a gush of dirty gray fluid and air from the mediastinum. The mediastinum was then widely opened, and the fluid removed. At this point, the blood pressure returned to normal and remained so thereafter. At the lower end of the esophagus, approximately 1 cm. above the diaphragm on the left anterolateral wall, was a 5-cm. vertical laceration, which involved the muscularis and mucosal coats; the edges, however, appeared entirely normal except for the reaction similar to that present throughout the mediastinum. There was no evidence of ulceration or tumor or stricture above or below the point of perforation. The mucosa was inverted with a running 000 catgut suture. The muscular layers were closed with interrupted catgut sutures. The pleural cavity was then irrigated with physiologic saline solution, and the lung re-expanded. One hundred thousand units of penicillin and 1 gm. of streptomycin were left in the pleural cavity. A No. 28 catheter was inserted through the tenth interspace for drainage. The chest wall was closed in layers, with interrupted catgut sutures and black silk to the skin.

The immediate postoperative course was uneventful. There was moderate drainage for 48 hours, after which the drainage tube ceased to function. The lung was well expanded immediately postoperatively and remained so. The temperature became normal on the 2nd postoperative day. The tube was left in place for 8 days because of a small posterior collection of fluid. Penicillin was continued for 8 days, and streptomycin for 4 days.

Administration of liquids was started on the 2nd postoperative day, and soft solids on the 5th day. On the 8th day, a small amount of methylene blue was given in water, and after 1 hour, the drainage within the intercostal tube showed a blue coloration. Because of this, open drainage of the posterior collection of fluid was performed. Two days later, a jejunostomy was performed, and the patient was fed through this for 10 days. From that time on there was no evidence of esophageal leakage. The patient was allowed to have a normal diet and was discharged home on June 5.

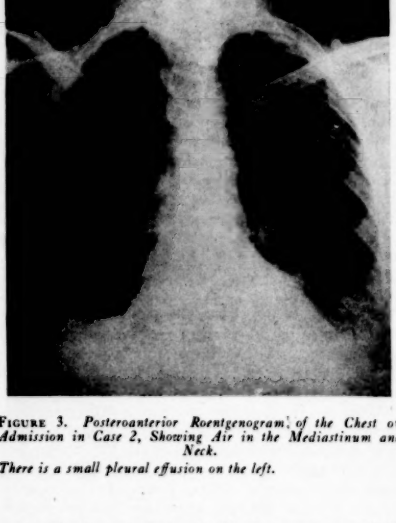

FIGURE 3. *Posteroanterior Roentgenogram of the Chest on Admission in Case 2, Showing Air in the Mediastinum and Neck.*

There is a small pleural effusion on the left.

FIGURE 4. *Posteroanterior Film of the Upper Abdomen Taken in the Upright Position on Admission in Case 2, Showing the Air in the Mediastinum behind the Heart.*

The jejunostomy tube was left in place for 1 month as a safeguard and then removed. The wound closed spontaneously. The empyema pocket closed rapidly, being completely obliterated in 6 weeks.

Postoperative follow-up study during the next 6 months showed no evidence of complications. The patient was eating well. There was no pain in the chest; the lungs were normally expanded, and the diaphragm functioned normally.

This case served to emphasize a number of points. The first, and most important, was that the diagnosis was made by the roentgenologist from the roentgenogram of the abdomen and chest. Nevertheless, it was not immediately appreciated that surgical treatment was possible, since it was believed

that this was a fatal lesion. However, the time allowed to pass was of no importance in this case, but the outcome could have been more serious if too much time had elapsed.

Secondly, the case showed, strikingly, the effect of mediastinal compression on the blood pressure. Immediately after the mediastinum was opened and the fluid and gas were released, the pressure returned to normal. It has been suggested[1, 3] that the early deaths are due to the mechanical compression of the vascular structures in the mediastinum, relief of which can be accomplished only by open drainage of the mediastinum. A reperforation at the site of repair apparently occurred in Case 2, but healing was rapid once rib-resection drainage of the empyema had been accomplished and jejunostomy feeding started. Generally, the results of operation, although not definitive, were most satisfactory and within a month of the onset, the patient was eating normally.

CASE 3. J. R., a 62-year-old man, was admitted to the Carney Hospital on November 12, 1948, with a history of severe chest pain of approximately 12 hours' duration. The patient stated that on the previous day he had consumed a large amount of beer while eating a moderate amount of food. At approximately 10 p.m. he noted severe gastric distress. Because of this distress, he attempted to vomit, and after some time, he had moderate success. He continued his efforts to make himself vomit, and during a period of severe retching, he suddenly noticed a burning sensation in the center of his chest. Because this sensation was so painful, the patient had to sit upright and lean forward. At the same time, he noted some sweating. His physician was called immediately.

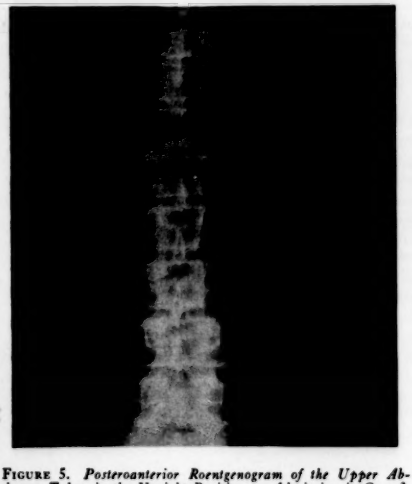

FIGURE 5. *Posteroanterior Roentgenogram of the Upper Abdomen Taken in the Upright Position on Admission in Case 3. This film clearly demonstrates the air behind the heart.*

Examination of the chest was negative. There was some tenderness with a slight spasm in the epigastrium. The blood pressure was 120/60, with a pulse of 100. The physician was unable to make a definite diagnosis and the patient was given morphine for pain. Re-examination on the following morning showed a further fall of the blood pressure, with an increase in the tenderness and spasm of the epigastrium. At this time, there was some dullness with diminished breath sounds at the left base, and because of this, the patient was hospitalized.

After admission, the course remained essentially unchanged. The patient preferred to sit up in bed and had a grunting-type of respiration, and there was increased spasm of the upper abdomen that appeared to be voluntary in type. There was slight subcutaneous emphysema in the right supraclavicular fossa.

The temperature was 103°F., the pulse 110, and the blood pressure 110/60.

X-ray examination, performed to rule out a perforated ulcer, showed air behind the heart (Fig. 5). A film of the chest taken at the same time showed widening of the mediastinum, with air in the mediastinum up to the neck (Fig. 6). The diagnosis of spontaneous perforation of the esophagus was made, and a thoracic surgeon was consulted. Immediate operation was advised and performed 12 hours after the onset.

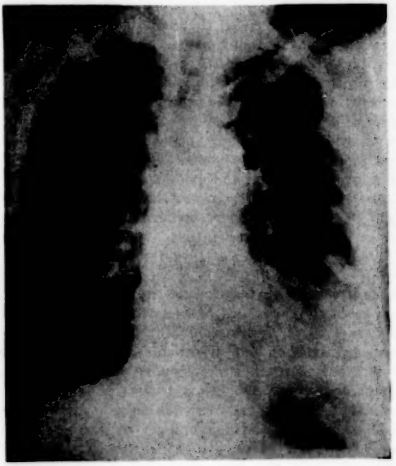

FIGURE 6. *Posteroanterior Roentgenogram of the Chest on Admission, Showing Air in the Lower Mediastinum.*

Under endotracheal nitrous oxide, oxygen and ether anesthesia, the left side of the thorax was entered through the bed of the ninth rib. Cloudy, odorless fluid was found when the pleural cavity was entered. The lung was retracted, and the mediastinum was seen to be bulging. Immediately on opening of the mediastinal pleura, air escaped, and a large amount of dirty, gray fluid that had a faintly foul odor was obtained. A large piece of cabbage was found in the mediastinum. At the lower end of the esophagus at the left anterolateral wall a 3.8-cm. laceration of a linear type was found. The mucosa pouted through the muscularis and appeared normal. The esophagus was mobilized at this

area, and the perforation closed with interrupted No. 000 silk sutures. The mucosa was closed in a double layer. A flap of mediastinal pleura was developed and sutured down over the area of laceration. The mediastinum was opened widely up to the arch of the aorta. The pleural cavity was irrigated with physiologic saline solution, and 100,000 units of penicillin and 1 gm. of streptomycin were left in the pleural cavity. A No. 28 catheter was inserted through the tenth interspace for drainage. The lung was re-expanded; the chest wall was closed in layers with interrupted No. 00 catgut sutures. The skin was closed with black silk.

The postoperative course was uneventful. Intramuscular administration of penicillin and streptomycin was continued postoperatively for 5 days. The intercostal tube drained satisfactorily for 48 hours and was removed after 72 hours in spite of a small amount of fluid that remained at the base posteriorly. The temperature remained normal from the 3rd day after operation. The patient was allowed out of bed on the 4th day. He was placed on a liquid diet from the 3rd day on, and was given a soft-solid diet on the 6th day. The patient was discharged on the 14th hospital day on a normal diet. The course thereafter remained satisfactory, and examination approximately 4 months after operation showed him to be in good physical condition. The lung was well expanded; he was taking a normal diet without difficulty.

This case represented the ideal of definitive treatment of this serious condition. Early diagnosis was possible because of early x-ray examination and the recognition of the significance of air in the mediastinum. Definitive operation was possible in spite of the patient's condition, and closure of the esophagus was adequate, allowing him to take a diet from the third day on. The possible presence of a foreign body in the mediastinum, such as previously ingested food, is demonstrated by this patient, and may further strengthen the indication for early surgical intervention.

Discussion

Spontaneous perforation of the presumably normal esophagus may not be as rare as the number of reported cases indicates. Since early diagnosis gives the best chance of satisfactory treatment, it is stressed that there is usually a characteristic symptomatology. One should always suspect this condition in any case in which severe pain in the lower chest or upper abdomen occurs during vomiting. Although there are no early characteristic physical signs, the finding of subcutaneous air in the neck in a patient with this story is diagnostic. However, even in the earliest stage after onset, x-ray study of the chest will show air or fluid behind the heart in the mediastinum. This, together with the characteristic story, should be diagnostic. A swallow of radio-opaque oil with fluoroscopic observation can be used if further proof of the diagnosis is desired.

Although one of the patients discussed above, as well as 3 in the literature, survived on a conservative routine of therapy, such an outcome should not be anticipated in most cases. The majority of the patients in the cases reported in the literature were treated conservatively, without survival. Early definitive operation aimed at closing of the perforation, relief of the mechanical compression of the mediastinum, expansion of the lung and drainage of the pleural cavity should prove to be more successful. With modern technics of anesthesia and thoracic surgery, aided by the antibiotics, operation generally provides the most satisfactory form of treatment for these seriously ill patients.

Summary

The clinical picture of spontaneous perforation of the normal esophagus is briefly reviewed, and reference to more complete studies is made.

The case histories of 3 patients successfully treated surgically are presented and discussed.

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HYPERPARATHYROIDISM WITH NEPHROLITHIASIS*

Report of a Case with a Parathyroid Tumor Located Within the Thymus

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BOSTON

THE existence of severe hyperparathyroidism without bone disease has been well established since it was first demonstrated in 1937 by Albright, Sulkowitch and Bloomberg.[1] The chief clinical manifestation of hyperparathyroidism in these patients consists of kidney stones or nephrocalcinosis, or both, without roentgenographic abnormalities of the bone or increased amounts of alkaline phosphatase in the blood. In the large series of cases of hyperparathyroidism studied by Albright and his co-workers[1, 2] kidney disease was more common than bone disease. The incidence of renal calculi was likewise high in the Mayo Clinic series reported by Keating and Cook,[3] unilateral or bilateral renal calculi being present in 18 of 24 cases of hyperparathyroidism; renal calculi or calcification of the kidneys was present in 92 per cent of their series. A subsequent report from the Mayo Clinic by Black[4] has emphasized the significant increase in the proved diagnosis of parathyroid adenoma when hyperparathyroidism is carefully and regularly sought in patients with renal lithiasis. Norris,[5] however, in a study of 322 reported cases of hyperparathyroidism, found bone involvement alone in 59 per cent and renal lithiasis or renal calcification without bone involvement in only 5 per cent. This is a striking discrepancy, which Norris himself ascribed to insufficient appreciation of the inter-relation between nephrolithiasis and hyperparathyroidism in many of the earlier cases. In any event, it is agreed that the commonest complication of hyperparathyroidism is precipitation of calcium salts in the urinary tract. This results from the associated hypercalcuria with the formation of calcium phosphate stones in alkaline urine or calcium oxalate stones in acid urine. Renal calcification or nephrocalcinosis results from the deposition of calcium casts in the kidney tubules or in the renal parenchyma.

The case reported below is noteworthy because it illustrates the frequently encountered difficulties in diagnosis when bone disease is absent, mild but prolonged hyperparathyroidism with striking recurrence of renal and ureteral calculi without bone involvement, an unusual location of a mediastinal parathyroid tumor, and the treatment of severe urinary sepsis complicating the nephrolithiasis by antibiotic and chemotherapeutic agents selected in accordance with in vitro sensitivity tests of the pathogenic organisms.

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Case Report

F. W. (B. I. H. 98960), an 18-year-old girl, first entered the Beth Israel Hospital on April 21, 1947, complaining of severe, colicky pain in the right flank of 48 hours' duration. Chills, fever (temperature of 104°F.), nausea and vomiting were present during the same period. She had had two similar attacks 3 and 9 months previously in both of which the symptoms had persisted for 48 hours. The past history was otherwise uneventful.

Physical examination revealed a well developed, acutely ill girl. The skin was hot and dry. The pupils were equal and reacted well to light and accommodation, and the extraocular reactions were normal. There were no abnormalities of the fundi. Examination of the ears, nose and throat revealed no abnormalities. There were no palpable masses, lymph nodes, thrills or abnormal pulsations in the neck. The thyroid gland was not enlarged. The breasts were normal. There were no palpable axillary or inguinal lymph nodes. The lungs were normal to palpation, percussion and auscultation. The heart was not enlarged; the sounds were forceful; the rhythm was regular, and there were no murmurs. The abdomen was soft and flat, with marked tenderness over the right costovertebral angle; no masses or organs were palpable. The extremities showed no edema. The knee jerks and ankle jerks were equal and active. The plantar reflexes were normal.

The temperature was 104°F., the pulse 130, and the respirations 30; the blood pressure was 120/70.

The urine was grossly bloody and contained numerous white cells. Culture of the bladder urine revealed *Pseudomonas aeruginosa, Aerobacter aerogenes* and *Bacterium alcaligenes*. The serum calcium was 11.0, 11.1 and 11.7 mg. per 100 cc. during the 8-day period from April 28 to May 6 (Table 1). Intravenous and retrograde pyelograms demonstrated a large, obstructing calculus in the pelvis of the right kidney and three small calculi in the lower calyx of the left kidney.

On the 4th hospital day a right pyelonephrolithotomy was done, with removal of the calculus. Chemical analysis of the stone showed it to consist of calcium phosphate.

Streptomycin in a dosage of 2 gm. daily, penicillin in a dosage of 300,000 units daily and sulfadiazine in a dosage of 2 gm. daily during the postoperative period had no effect on the pyuria or bacilluria. The patient was discharged on May 28, symptom-free and afebrile but with the urine still containing *Escherichia coli* and *A. aerogenes*. No attempt to remove the stones in the left kidney was made. The significance of the slight hypercalcemia was not appreciated at this time.

On June 21 the patient was readmitted because of left-flank pain, chills, fever (temperature of 104°F.), malaise, nausea and vomiting. She was acutely ill and markedly dehydrated. There was tenderness over the left costovertebral angle. Urinalysis revealed pyuria and bacilluria. Culture of the urine showed *Esch. coli* and *A. aerogenes*. After 4 days' treatment with 2 gm. of streptomycin daily and 2 gm. of sulfadiazine daily the patient became afebrile and symptom free; the urine, however, remained infected with the same organisms. She was discharged on the 11th hospital day.

Five days after discharge the patient was again readmitted because of chills, fever, left-costovertebral-angle pain, nausea

and vomiting. The temperature was 104.8°F., and the pulse 146. Retrograde pyelograms revealed two ureteral calculi in the region of the left ureterovesical junction and a larger stone in the left ureter at the level of the lower end of the sacrum. The lower ureteral calculi were removed by cystoscopic manipulation. Urine cultures at this time revealed *Esch. coli*, *A. aerogenes* and *Ps. aeruginosa*. These organisms were resistant to streptomycin, penicillin, sulfadiazine and Mandelamine, both clinically and in vitro. The patient left

tient's condition precluded any further operative manipulation. Culture of the urine revealed *A. aerogenes* and *Ps. aeruginosa*, which were still resistant to penicillin, streptomycin, sulfadiazine and sulfamethazine[6] by in vitro sensitivity tests.[7] However, Nu 445 (3, 4-dimethyl-5-sulfanilamido-isoxazole) in 0.75 per cent concentration and sulfathiazole in 0.1 per cent concentration were bactericidal in vitro.[8] Accordingly, these drugs were administered during the postoperative period. On this therapy the temperature

TABLE 1. *Pertinent Data on First Admission.*

Date	Nonprotein Nitrogen	Total Protein	Serum Calcium	Serum Phosphorus	Alkaline Phosphatase	Ionized Calcium
1947	mg./100 cc.	gm./100 cc.	mg./100 cc.	mg./100 cc.	units/100 cc.	mg./100 cc.
4/28	45	—	11.0	1.7	7.1	—
4/30	40	—	11.1	3.3	—	—
5/6	34	7.04	11.7	3.7	2.9	5.25

the hospital after 10 days, free of pain, but with an infected urine and a stone still present in the lower third of the left ureter.

She remained asymptomatic for 7 months, after which she again experienced an attack of left-flank pain associated with chills, fever (temperature of 103.6°F.), nausea and vomiting. She was readmitted on February 25, 1948, acutely ill and markedly dehydrated. Excretory pyelograms disclosed

gradually returned to normal, with clinical improvement. The bladder urine was sterile, but urine from the left nephrostomy showed *A. aerogenes*, *Esch. coli* and *Ps. aeruginosa* on culture, although there was a marked decrease in the number of bacteria.

The rapid formation of urinary calculi led to a search for hyperparathyroidism. Serum calcium determinations during the following 27 days showed values fluctuating between

TABLE 2. *Pertinent Data on Fourth Admission.*

Date	Nonprotein Nitrogen	Total Protein	Serum Calcium	Serum Phosphorus	Alkaline Phosphatase	Ionized Calcium
1948	mg./100 cc.	gm./100 cc.	mg./100 cc.	mg./100 cc.	units/100 cc.	mg./100 cc.
2/27	40		12	1.7	3.9	
2/28	47	6.19	11.5	2.0		5.6
3/1			8.6	2.5	4.5	
3/3	40		9.1	3.0		
3/6	30		9.1	3.0		
3/7			8.6			
3/9			10.7	2.4		
3/11			10.6			
3/24			12.6			
3/25			12.7	3.5	3.3	
3/29			12.3	3.3		
4/3*			12.0	3.6		
4/6			11.3			
4/8			12.2	2.3		
4/15			11.7	2.8		
4/23			12.5			
5/11†			8.3	3.3	3.8	
5/12			8.2			
5/13	44	6.56	8.9	3.8	5.4	4.1
5/14		7.52	9.6	3.1		4.1
5/17		7.30	8.9	3.6	3.9	3.8
5/18			9.2	3.9		
5/19			9.1	3.6		
5/20	36		10.4	4.3		
5/24		7.70	9.6	4.4	3.2	4.0
5/26		8.00	8.5	4.0	2.9	3.4
5/28		8.47	9.6	4.0	3.6	3.7
6/17			9.9	3.6		
6/24			9.7			
6/29			9.7			
7/7			10.0	3.8		
7/14			9.8	4.0		
7/27	31		9.7	3.1	2.1	
8/3	34		9.8	3.8		
8/19	27		9.7	4.2		

*Cervical exploration performed on preceding day.
†Mediastinal operation (removal of parathyroid tumor) performed on preceding day.

a large obstructing calculus in the left renal pelvis and multiple smaller calculi in the lower calyx. A ureteral catheter could not be passed by the stone in the renal pelvis. The clinical course was characterized by recurrent chills and persistent fever, the temperature often reaching 105°F. A left pyelonephrolithotomy and nephrostomy were done on the morning after admission. The kidney was edematous, and its surface studded with small abscesses. The large stone in the pelvis was easily located and removed. The smaller calculi in the lower calyx were not removed because the pa-

12.7 and 8.6 mg. per 100 cc. (Table 2). The serum inorganic phosphorus levels ranged from 3.6 to 1.7 mg. per 100 cc. (Table 2). The Sulkowitch test, performed on urine obtained at 8-hour intervals each day for 14 days, varied from ++ to ++++ while the patient was on a low-calcium diet (0.22 gm. of calcium per 2000 calories). Roentgenograms of the skeletal system and teeth showed no decalcification or cyst formation. The calculus removed from the

*Dr. Fritz H. Schweinburg generously co-operated in the performance of the bacteriologic and in vitro sensitivity studies.

kidney was examined by Dr. E. L. Prien, utilizing the method of optical crystallography, and found to consist of 95 per cent calcium phosphate.[8]

In view of the recurrent nephrolithiasis, hypercalcemia and hypophosphatemia and the nature of the removed stone a diagnosis of hyperparathyroidism was made, and parathyroidectomy undertaken.

The first operation consisted of a cervical exploration by Dr. J. Fine on April 2, 1948. Both thyroid lobes were fully exposed and examined without disclosure of any abnormalities. Exploration posterior to the trachea and esophagus and of all cervical tissues up to the hyoid bone and down to the jugular notch revealed no evidence of parathyroid tumor.

After this operation the abnormal values of serum calcium and inorganic phosphorus persisted (Table 2). The urinary infection was treated in succession with 3 gm. of Mandelamine, 6 gm. of sulfamethazine, 2 gm. of sulfathiazole and 6 gm. of sulfathaladine daily, with some clinical and bacteriologic improvement but without rendering the urine sterile. A second operation for the relief of the hyperparathyroidism was therefore undertaken on May 10 by Dr. Fine. The anterior mediastinum was explored through a sternum-splitting incision. No parathyroid tumor was found in the plane anterior to the thymus. Accordingly, the thymus itself was dissected free from the underlying great veins. The lower pole of the left lobe was enlarged and on palpation contained a firm, discrete nodule about 5 mm. in diameter buried in its substance. The thymus with its contained nodule was therefore removed. Examination of the nodule by frozen section showed it to consist of parathyroid tissue. Further exploration of the anterior mediastinum from the thoracic inlet to the top of the pericardium, anterior and posterior to the innominate veins and superior cava, disclosed no further evidence of parathyroid tissue.

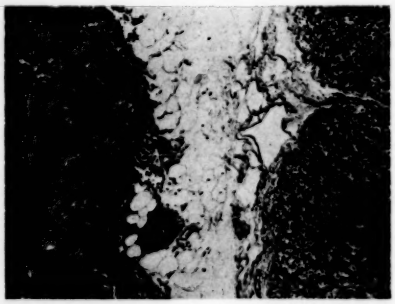

FIGURE 1. *Section Showing the Thymus at the Left and the Parathyroid Nodule at the Right.*
Note the acinar and tubular arrangement of the parathyroid cells and basal orientation of the nuclei (x 100).

On pathological examination the thymus was roughly triangular in shape and measured 3.5 cm. in width, 3.5 cm. in length and 0.4 cm. in thickness, and had the appearance of fibrofatty tissue. Near one of the angles a small nodular mass with the consistence of a lymph node was palpated. When dissected it had the shape and size of a small bean, measuring 4.5 by 4.0 by 5.5 mm. This was the same parathyroid nodule examined by frozen section at operation. Microscopical examination of the nodule showed a thin, incomplete fibrous-tissue capsule No fat cells were enclosed in the section. The nodule was fairly vascular throughout. The epithelial cells comprising the nodule were present in bands and nests. There was a rich reticular and capillary network, free of congestion. The bulk of the epithelial cells were very similar in appearance. In the smaller nests the peripheral cells in contact with the reticular stroma tended to become polarized. Occasionally, the polarized cells surrounded a lumen measuring 12 to 20 microns in diameter and containing in some areas deeply eosinophilic staining nongranular material. In many nests, particularly the larger ones, there was no tendency to polarization. The epithelial cells generally showed a thin but distinct cell wall, which was most obvious in the polarized cells. Their cytoplasm was quite uniform in appearance, finely granular, pale and acidophilic. The nuclei of the epithelial cells were round to oval and showed a fairly uniform size, measuring 10 to 15 microns. There was abundant chromatin arranged in a uniform, coarsely granular pattern in a nongranular, fainter basophilic background. About 10 per cent of the nuclei had one or more nucleoli. No mitoses were seen. In occasional small areas the epithelial cells were larger with a paler, looser cytoplasm. The nuclei of these cells were larger and paler with more prominent nucleoli. These cells showed little polarization. They resembled but were not typical "wasserhelle" cells. Scattered through the sections were individual small clumps of "oxyphil" cells, which were more rounded and larger than the majority of the epithelial cells of the nodule. These cells had a more eosinophilic and slightly granular cytoplasm, with dark, round pyknotic nuclei (Fig. 1 and 2).

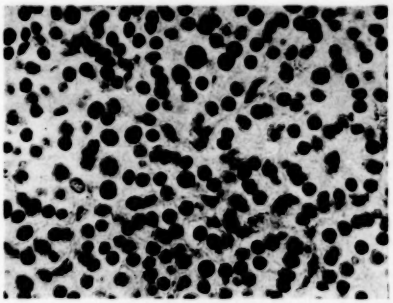

FIGURE 2. *Section of Parathyroid "Tumor," Showing Moderate Variation in Cell Size and Density of Staining of the Nuclei (x 500).*

After operation the patient received a high-calcium diet with dihydrotachysterol (A.T. 10) for 5 days to prevent tetany. The serum calcium on the 1st postoperative day was 8.3 mg. per 100 cc. of blood, and the serum inorganic phosphorus 3.3 mg. per 100 cc. of blood (Table 2). Serum calcium values during the subsequent 3-week period varied between 8.2 mg. and 9.6 mg., and the serum phosphorus ranged between 3.3 and 3.8 mg. per 100 cc. Clinically, the immediate postoperative course was uneventful, although the urine still remained infected.

As a result of the recurrent nephrolithiasis, surgical manipulation and persistent urinary infection, a complete stricture developed at the left ureteropelvic junction. Repeated dilatations over a 3-month period were unsuccessful in overcoming the obstruction. The patient continued to have attacks of chills and fever, although no new calculi were observed. Cultures of the urine from the right kidney and bladder showed many colonies of *Ps. aeruginosa* and *A. aerogenes*, whereas the cultures from the left nephrostomy tube showed *Ps. aeruginosa*, *Esch. coli*, *A. aerogenes*, *Streptococcus faecalis* and paracolon bacilli. These organisms were resistant to sulfanilamide, sulfathiazole, sulfadiazine, sulfamethazine, NU 445, penicillin and streptomycin in vitro.

However, all strains except *Ps. aeruginosa* were very sensitive to aureomycin.*

Aureomycin in a dosage of 10 mg. was given intramuscularly twice daily for 10 days without reaction except for pain at the site of injection. Twenty-four hours after the initiation of therapy with aureomycin, urine from the right kidney and bladder was found sterile by culture (Fig. 3). Urine from the nephrostomy tube still produced a heavy growth of *Ps. aeruginosa*. Irrigations of the left renal pelvis with

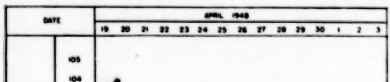

FIGURE 3. *Effect of Aureomycin before Nephrectomy.*

aureomycin (1 mg. in 10 cc. of physiologic saline solution) through the nephrostomy were not bactericidal. After termination of therapy, urine from the right kidney and bladder continued to be sterile. Urine from the left kidney, however, showed a moderate growth of *Ps. aeruginosa*.

Two weeks later the patient again experienced pain in the left flank associated with chills, fever (temperature of 103°F.), nausea and vomiting. The infection again involved both

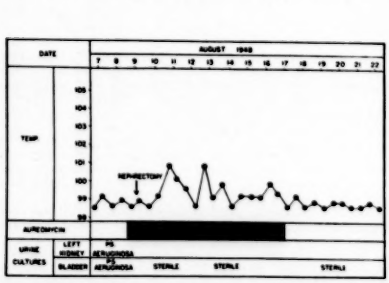

FIGURE 4. *Effect of Aureomycin after Nephrectomy.*

kidneys and bladder, and there were positive cultures of *Ps. aeruginosa* and *Esch. coli* in the urine.

Because of the persistent urinary-tract infection and the multiple calculi in the lower calyx of the left kidney, an attempt was made to correct the obstruction at the ureteropelvic junction. At operation the severe inflammatory reaction, dense adhesions and an intrarenal location of the pelvis rendered plastic procedures impossible so that a nephrectomy was performed.

After nephrectomy, the patient received 20 mg. of aureomycin intramuscularly twice daily for the first 3 days, and then 10 mg. twice daily for the next 4 days; streptomycin† in a dosage of 2.0 gm. was also given daily. Urine from the right kidney and bladder became sterile in 24 hours and remained so throughout the hospital stay. The postoperative course was uneventful, the temperature returning to normal in 3 days. Four weeks postoperatively the patient was asymptomatic and free of urinary infection, as shown by a clear urine, which was free of abnormalities of the sediment or bacterial growth (Fig. 4).

The patient was seen in the Out-Patient Department 4 months after removal of the parathyroid tumor. She was asymptomatic, and physical examination showed no abnormalities. The serum calcium was 8.2 mg., serum phosphorus 3.2 mg., total protein 6.8 gm., and ionized calcium 3.5 mg. per 100 cc. The urine was sterile on culture and contained no abnormalities of the sediment. By January, 1949 (8 months after parathyroidectomy), she had gained 22 pounds in weight. A roentgenogram of the genitourinary tract at this time revealed no calculi. The urine was sterile on culture. The serum calcium measured 9.9 mg., serum phosphorus 3.4 mg., and total protein 6.7 gm. per 100 cc., with an ionized calcium of 4.7 mg. The serum calcium 10 months after parathyroidectomy was 9.5 mg. per 100 cc.

In this case of hyperparathyroidism, recurrent renal and ureteral calculi were complicated by severe bilateral urinary-tract infection. On the first admission a large obstructing calculus in the pelvis of the right kidney and three small calculi in the lower calyx of the left kidney were demonstrated, in association with marked pyuria and bacilluria. Serum calcium and phosphorus determinations revealed mild hypercalcemia and hypophosphatemia. The stone in the right kidney was removed surgically, but the stones in the left kidney were untouched. Streptomycin, penicillin and sulfadiazine had no effect on the urinary-tract infection. Two months after the first admission the patient was readmitted because of recurrent urinary sepsis. On this admission two ureteral calculi were removed from the lower end of the left ureter by cystoscopic manipulation. The organisms present in the urine were resistant to streptomycin, penicillin, sulfadiazine and Mandelamine both clinically and in vitro. The patient was discharged with an infected urine and a left ureteral stone. Seven months later she was readmitted with recurrent symptoms of urinary infection. A large obstructing calculus in the pelvis of the left kidney was surgically removed, but multiple smaller calculi in the lower calyx of the kidney were left. Optical crystallography of the removed calculus showed it to consist of calcium phosphate. Urine culture still revealed a marked pyuria and bacilluria. In vitro sensitivity tests showed NU 445 and sulfathiazole to be bactericidal to these organisms. These drugs temporarily cleared the urinary infection of the right kidney, but urine from the left nephrostomy continued to show a heavy growth of bacteria. At this point a clinical diagnosis of hyperparathyroidism was established by the finding of hypercalcemia and hypophosphatemia and hypercalcuria. A hyperfunctioning parathyroid tumor was discovered, after a negative exploration of the neck, in the substance of the thymus gland.

*This antibiotic was supplied by the Lederle Laboratories Division of the American Cyanamid Company, New York City.

†The strain of *Ps. aeruginosa* isolated from the bladder was resistant in vitro to streptomycin.

The serum calcium returned to normal on the first postoperative day and subsequently remained normal.

During all hospital admissions the urinary infection proved resistant in vitro and clinically to penicillin, streptomycin, sulfadiazine, sulfamethazine and Mandelamine. NU 445 and sulfathiazole had a transitory beneficial effect. Aureomycin[9] quickly cleared the infection of the right kidney and bladder (Fig. 3). However, the left kidney, because of an impassable stricture at the ureteropelvic junction and the presence of calculi remained infected and caused severe clinical symptoms until removed.

Discussion

Although the number of reported cases of hyperfunctioning parathyroid adenoma now numbers almost 400 and the essential features of the syndrome have been well described, the present case illustrates the difficulties of achieving diagnosis and cure when the tumor is small, obscurely located and associated with minimal hyperfunction.

Albright and Reifenstein[2] have pointed out that hyperparathyroidism may exist in 4 clinical forms, tabularly represented as follows:

	Bone Disease	Kidney Disease
(A)	Present	Absent
(B)	Present	Present
(C)	Absent	Present
(D)	Absent	Absent

Hyperparathyroidism without bone or kidney disease has been reported but once; in this form diagnosis must initially depend upon characteristic blood chemical findings and clinically could only be suspected from the symptom of polyuria. The other forms of hyperparathyroidism are common and offer diagnostic clues either in the presence of bone disease such as osteitis fibrosa cystica or kidney disease as nephrolithiasis or, more rarely, as renal calcification.

The starting point in the diagnosis of hyperparathyroidism is a problem in quantitative chemistry. One must know the precise range of normal values for the method utilized in the hospital laboratory. If the total protein level is normal, serum calcium values above 11 mg. per 100 cc. must be regarded as suspect when associated with nephrolithiasis, osteoporosis, osteitis fibrosa cystica or unexplained polyuria. If there is simultaneous depression of the serum phosphorus level the diagnosis becomes increasingly certain.

It is clear that there is little diagnostic problem in cases in which the serum calcium is above 12 mg. with characteristic bone changes. Difficulties arise, however, in cases like the present, in which bone changes were completely absent and the serum calcium persistently hovered about 11 mg. per 100 cc., occasionally dropping to completely normal values (Table 2) or occasionally rising to slightly abnormal values. In these situations the use of the Sulkowitch test as an index of calcuria is important, since the demonstration of a high-calcium output in the urine, with normal or slightly elevated serum calcium, should lead to further search for hyperparathyroidism. Several factors influence the interpretation of the Sulkowitch test, especially the previous diet, the concentration of the urine, the age of the patient and the presence or absence of renal disease. For this reason serial tests are most informative, the simplicity of the test lending itself readily to this purpose.

The degree of elevation of the serum calcium and consequently the degree of depression of the serum phosphorus is roughly proportional to the size of the tumor[10] except in larger adenomas, when the proportionality is less. The smallness of the tumor in the present case was entirely consistent with the minimal elevations of the serum calcium observed at the first and fourth admissions. The tumor size, however, does not explain the sudden decline of the calcium values to normal or subnormal values during the fourth admission (Table 2) for a period of six days, followed by a return to slight hypercalcemia. An increased phosphate intake in the diet could explain such a decrease but would be accompanied by an elevation of the serum phosphorus level. Since this did not occur the explanation is more likely to be found in the intravenous infusion of saline solutions, which were given during this period because of the patient's condition. Physiologic saline solution, according to Albright and Reifenstein,[2] is a useful agent in parathyroid poisoning, presumably through a temporary effect in lowering the blood calcium.

Although small tumors do not elevate the blood calcium very much, this minimal elevation is entirely adequate for the production of nephrolithiasis in the severe form exhibited by this patient with both multiple stones, a rapid rate of stone formation and severely damaging renal infection.

Whereas the reported figures of parathyroid adenomas that are completely mediastinal have varied from 7 to 17 per cent,[4, 5, 11] the number that are completely intrathymic is extremely small. Cope[11] has reported only 3 such tumors in his large series, whereas Norris,[8] in his collective review of 322 cases, mentions 9. Embryologically, the intrathymic location is readily explicable because the lower parathyroid glands develop in close proximity to the thymus gland, descending partially with it but usually dropping off opposite the lower pole of the thyroid gland. Occasionally, however, the parathyroid glands grow down into the mediastinum adjacent to or within the body of the thymus gland.

The nature of the parathyroid lesion in this case was clearly that of a hyperfunctioning tumor or adenoma, since removal of a single, encapsulated nodule resulted in rapid and permanent disappearance of the signs and symptoms of hyperpara-

thyroidism. Hyperparathyroidism resulting from primary hyperplasia always involves all four parathyroid glands and therefore will not remit with removal of a single gland.

The early diagnosis of hyperparathyroidism is particularly important because the nephrolithiasis or nephrocalcinosis frequently associated with the disease may lead to irreparable kidney damage or prolonged renal infection with loss of a kidney, as illustrated by the case reported above. Chemotherapy based on in vitro sensitivity tests, combined with relief of obstruction and removal of an infected kidney, led to eventual clearing of the sepsis of the genitourinary tract.

Summary

A case of hyperparathyroidism with nephrolithiasis and without bone disease caused by a small intrathymic parathyroid tumor is reported. Complete clinical cure of the hyperparathyroidism followed removal of the parathyroid lesion.

The difficulties in the clinical diagnosis are discussed.

Genitourinary sepsis of severe degree was the chief complication. This sepsis was eventually controlled by nephrectomy and the selection of appropriate antibiotics on the basis of in vitro sensitivity tests.

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CONDITIONED-REFLEX TREATMENT OF ALCOHOLISM

II. The Risks of Its Application, Its Indications, Contraindications and Psychotherapeutic Aspects

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In the first article about the conditioned-reflex therapy its rationale and technic were discussed.[1] The purpose of the present study is to show the risks, indications, contraindications, efficacy and psychotherapeutic aspects.

To establish a reflex association between alcoholic beverages and vomiting, emetine hydrochloride is used as the unconditioned stimulus. The pharmacologic interest in emetine started with its use for treatment of amebic dysentery, liver abscesses and alveolar pyorrhea.

Emetine is one of the alkaloids of ipecacuanha. Its pharmacologic properties were the object of extensive studies during the greater part of the nineteenth century. However, not until 1893 did Paul and Cownley[2] demonstrate that the so-called emetine of previous workers was in reality a mixture of two alkaloids, emetine and another one, which they called "cephaeline."

Two years later, the pure emetine was for the first time investigated by Wild,[3] who studied its emetic and other properties. He found that it lowered the blood pressure and in excessive doses caused an arrest of the heart in diastole.

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The mode of excretion of emetine could not be determined. No traces were found in gastric or intestinal contents or in the urine. Baermann and Heinemann[4] have stated that "with moderate sized doses of 60 to 150 mg. there are no symptoms":

> If 120 to 150 mg. are given in daily repeated injections, there appear, after three or four injections, malaise, lassitude, slight vertigo and loss of appetite. These symptoms disappear in from 24 to 72 hours after the emetine has been discontinued.

Vedder[5] called attention to the fact that rabbits died after small intravenous doses of emetine and advised strongly against the intravenous application in human beings.

Other investigators described the gastrointestinal side effects such as nausea, vomiting and diarrhea.

Levy and Rowntree[6] cited several observers with 20 case histories. One of these patients received a total dosage of 1.45 gm. (24 gr.), another 1.28 gm. (21 gr.), and a third 1.75 gm. (29 gr.). The first 2 patients recovered although not without a transitory phase of diarrhea and a mild peripheral neuritis.

A recent paper by Dack and Moloshok[7] cited Heilig and Visveswar, who "failed to observe any significant alteration in the EKG, blood pressure

or orthodiagram of 14 patients treated with twelve intramuscular injections of 1 grain (0.06 gm.) of emetine hydrochloride daily." Hardgrove and Smith, cited in the same paper, observed in a series of 72 patients only 1 serious cardiac effect. They concluded that emetine hydrochloride in therapeutic doses produced only minor and transient electrocardiographic changes and that there was little risk involved in the use of emetine hydrochloride if electrocardiograms were taken during the course of treatment and the patient was kept in bed.

Dack and Moloshok discussed further their own observations of 9 patients, who were treated for amebic dysentery with emetine hydrochloride. The total dose ranged from 0.45 to 1.42 gm. (7 to 22 gr.). The neuromuscular manifestations of toxicity such as general muscular aching and weakness, tremor of the hands and dizziness usually appeared during the period of administration of emetine hydrochloride. In 8 of these cases, however, an abnormal electrocardiogram was not demonstrated until two to twenty-one days after the last injection of emetine.

The clinical examination of the cardiovascular system in these 9 cases did not show strikingly abnormal findings. Three patients displayed moderate tachycardia at rest and after mild effort. In 1 patient it was associated with presystolic gallop rhythm. Another patient complained of a mild precordial discomfort. In 5 cases there was dyspnea and fatigue of various degrees on exertion. None of the patients showed any abnormality in the size or configuration of the heart by x-ray examination. There was no significant lowering of the blood pressure.

In 3 cases diarrhea occurred during the course of treatment. The symptoms disappeared spontaneously when the use of emetine was discontinued.

The authors recommend: absolute rest in bed during the course of treatment; daily recordings of the pulse rate at frequent intervals (tachycardia may be the first clinical sign of toxic effect); the patient should be examined and questioned at least daily for diarrhea, fatigue, dyspnea on exertion, muscular tremors or weakness and dizziness; an electrocardiogram should be taken before the treatment is instituted, after the fifth grain, at the completion of the course of the treatment and one week later (use of the drug should be discontinued if significant changes are found); emetine should not be used in the presence of organic heart disease and should be used with great caution in patients who are anemic and debilitated.

It may be recalled that the first report about the use of emetine for treatment of alcohol addiction was presented by Voegtlin[8] in 1940.

Less than two years later the conditioned-reflex therapy by means of emetine was started for the first time on the eastern seaboard at the Washingtonian Hospital in Boston; 282 patients have been treated to date.* Their ages ranged from seventeen to sixty-four years. The total dose of emetine hydrochloride, as injected subcutaneously, during the initial series of six to seven daily sessions, varied from 0.5 gm. (7.5 gr.) to 0.85 gm. (13¾ gr.). Lately, it has been found that a series consisting of six sessions suffices to establish the reflex. This reduced the total dose to 0.675 gm. (11¼ gr.). As mentioned in the previous article[1] the patient receives prior to the injection a capsule containing 60 to 150 mg. (1 to 2½ gr.) of additional emetine hydrochloride by mouth with 1 to 3 glasses of water. It is assumed that very little of this additional emetine is absorbed because, after the dissolution of the capsule, the emetine becomes dissolved or suspended in the water contained in the stomach, most of which is vomited as soon as the emesis begins.

All but a few of the 282 patients treated reacted after two to four injections with diarrhea, mostly of a mild degree (two to five bowel movements daily). Only nine patients (3.19 per cent) claimed ten to fifteen bowel movements daily. Discontinuance of emetine injections for one to several days, combined with generous doses of kaopectate, stopped the diarrhea. The initial series was continued, if necessary, with additional intermissions. Ten patients complained of cramping pain of the intestines or genitals, but only during the treatment sessions, when the emetine (and pilocarpine?) action was at its peak. The end of the treatment session, sometimes with the aid of a hot-water bottle, terminated the spasms.

Other side effects of emetine application were the neuromuscular disturbances. Ten to fourteen days after the initial series approximately 60 per cent of all patients treated displayed general muscular weakness and aching, especially in the lower extremities. The degree of these neuromuscular manifestations was light to moderate. The patients were able to walk and to climb and descend stairs without too much inconvenience. In only 2 cases (0.7 per cent) — both female patients, incidentally — the degree of the neuromuscular involvement was such that the patients were, for two or three weeks, able to walk on level ground only. All these neuromuscular manifestations, however, were safely overcome, at the latest, after several weeks of convalescence. Thus, all the side effects described above were mild.

Only 5 patients out of 282 treated with emetine (1.43 per cent) reacted with cardiovascular manifestations of any degree of severity.

One of these patients was a thirty-year-old, husky man. His electrocardiogram was described by the cardiologist as indicating a moderate degree of myocardial fibrosis — not extensive enough to

*This figure includes female patients who had to be treated outside the Washingtonian Hospital because of the lack of facilities for such patients.

represent a contraindication for conditioned-reflex therapy. The initial series of the treatment involved seven injections with a total dose of 0.54 gm. (9 gr.) of injected emetine, followed by an additional injection of 0.15 gm. (2½ gr.) of injected emetine nine days later. During that whole period this patient did not display any tachycardia, drop in blood pressure, arrhythmia, gastrointestinal or neuromuscular side effects. Fifteen days after the initial series, the patient traveled to a neighboring state for some urgent business. For two days, he was exposed to relatively marked physical strain. Three days later he complained of weakness of the lower extremities, shortness of breath and occasional precordial distress. An electrocardiogram and clinical examination revealed sinus tachycardia. Five days later he was definitely better. His pulse was still 140, but the blood pressure rose to 110 systolic, 80 diastolic. Another five days later, the pulse slowed down to 110; eight days later it was 96, and the blood pressure was 125 systolic, 70 diastolic. Although the electrocardiogram still showed abnormalities, it also revealed progressive improvement in the condition of the myocardium. There was still gallop rhythm. From then on the blood pressure remained normal. The only abnormal sign — the gallop rhythm — disappeared finally three weeks later.

Another patient, an asthenic, fifty-year-old man with an asthmatic bronchitis and a positive blood Hinton reaction, felt, thirteen days after a total dose of 0.8 gm. (13 gr.), dizzy and lightheaded for one day. Aside from this side effect, he complained of muscular weakness and aching for twenty-three days.

Several hours after the first emetine injection of 55 mg. a third patient, a slender, run-down, fifty-seven-year-old man, showed severe gastrointestinal and circulatory manifestations, such as severe, watery diarrhea, pallor, a very small, rapid pulse (120 per minute), cramps in both legs and cold extremities. Fifteen minutes after caffeine injection he felt more comfortable, and the pulse was 96 and better filled. The blood pressure was 120 systolic, 80 diastolic. The rest of the series of injections was well tolerated and provoked no immediate untoward reactions. However, a week after the end of the series, the patient complained of fainting spells and palpitations, shortness of breath, tachycardia and muscular weakness. An electrocardiogram showed auricular fibrillation. Rest in bed, digitalis and ammonium chloride brought the heart back to normalcy. From then on the patient was able to tolerate the additional reinforcements without any toxic manifestations.

Sometimes lack of judgment and restlessness, not at all a rare phenomenon in alcoholic patients, may prevent a patient in need of rest in bed from following medical advice. Such nonco-operation may prove fatal, as the following case history illustrates.

A 35-year-old unusually obese man (weighing 241 lb.), with a blood pressure of 106/76, negative liver tests and an electrocardiogram within normal limits, underwent the initial series of the conditioned-reflex treatment after recovery from a bout of drinking lasting 6 weeks. The total dose of injected emetine was 0.77 gm (12¾ gr.). He claimed that he was too restless to stay in bed during the days of the initial series and was even more restless after that. He insisted upon leaving the hospital only 2 days after completing the initial series and on resuming his occupation as a very active salesman.

One week after discharge from the hospital, tachycardia and gallop rhythm developed. Again, he refused hospitalization, for business reasons, for another 2 days. Finally, he returned to the hospital with complaints of general weakness and shortness of breath. Physical examination revealed a heart enlarged in all diameters, with the apical beat in the sixth interspace; the heart rate was 110 and regular, and the blood pressure 110/80. From then on the cardiac failure progressed rapidly. Approximately 12 hours after readmission the patient died.

Kattwinkel[9] has recently reported an additional fatal case. Fortunately, such a fatal termination occurred in only 2 cases out of 282 treated, representing a mortality of 0.7 per cent.

To reduce to a minimum and, if possible to eliminate the risks of toxic manifestations altogether, three modifications are now applied. In the first place the initial series of injections consists now of only six, the total initial dose of injected emetine thus being reduced to 0.675 gm. (11¼ gr.). Secondly, pilocarpine has been eliminated from the injectable emetine solution. Thirdly, the conditioned reflex therapy is applied only to patients who accept the plan of rest in bed and hospitalization for an additional four weeks after completing the initial series of treatments. The number of patients who have complied with this stipulation is so far too small to form a basis for conclusions. It has been reassuring, however, that no cardiovascular side effects have developed.

The primary research plan at the Washingtonian Hospital is either to modify emetine chemically or to substitute for it another suitable emetic, with the goal of preventing not only the cardiovascular complications but also the side effects.

A discussion of the efficacy of the conditioned-reflex therapy would be incomplete without mention of the question of recidivism. The relapse seems to be caused in some cases by external and in others by intrinsic factors. The first group may be benefited either by single reinforcements or by a full retreatment including the initial series. The prognosis for such patients is good, probably because of the very fact that it takes considerable maturity and determination to return for additional treatment.

One patient who relapsed largely for external reasons was a man in his forties, in a responsible position, who clearly realized the necessity for total abstinence from alcoholic beverages and who did his best to obtain it by undergoing a course of in-

dividual psychotherapy. After several failures to prevent relapses, his therapist referred him for conditioned-reflex therapy. When the patient completed his initial series of the conditioned-reflex therapy, he was advised to return four weeks later for his first reinforcement. Circumstances delayed his return by an additional three months. As it happened he was able to abstain from drinking for those four months, but when he again, for external reasons, postponed his second reinforcement he relapsed. He then accepted the suggestion of a full retreatment, and six years later was able to report that he was apparently completely cured.

Intrinsic reasons for relapse observed in these patients include an ambivalent attitude regarding abstinence, poor rapport with the therapist (father hostility) and subsequent rejection of follow-up psychotherapy and neurotic difficulties in facing life without the crutch — alcohol. Such recidivists have naturally a poor prognosis.

The indications for the conditioned-reflex therapy may be conceived in a twofold way. From a narrow point of view, it seems plausible to state that it should be given to patients with whom other therapeutic approaches have failed. However, in view of the unusually high success of the conditioned-reflex therapy, as compared with other kinds of therapy, a broader conception is justified — that is, all patients who are physically and psychologically eligible should actually have the opportunity to avail themselves of it. The latter point of view will be even more acceptable if the working hypothesis of the autonomous, self-perpetuating, abnormal reflex of addictive drinking is kept in mind. The contraindications, which have been listed elsewhere,[10] are briefly as follows: I. Q. markedly below 100; constitutional psychopathy; lack of intellectual or emotional ability to recognize the necessity of permanent abstinence; record of serious criminal offenses committed in a state of sobriety; combination of alcohol and drug addiction; and acute psychosis.

Physical contraindications include disturbances of the cardiovascular-renal system, active tuberculosis of the lungs, active peptic ulcer and cirrhosis of the liver.

Efficacy

The efficacy of the treatment is demonstrated by the following statistics: 282 patients have undergone the conditioned-reflex therapy since February, 1942, and 7 of these did not finish the initial series, the total thus being reduced to 275. Results have been verified, in most cases, by periodic, personal contacts in the form of weekly interviews, reinforcements, semimonthly abstinence-club meetings and, for patients living in remote parts of the United States and Canada, by correspondence, which is rechecked by social workers, local physicians, probation officers and relatives.

Out of these 275 patients no follow-up information is available on about 30 patients, leaving a remainder of 245. Of these, 125 are still total abstainers. This figure includes 9 who relapsed once and had to be retreated. Of the 125 patients, 21 have been totally abstinent for six to seven years; 37 have been abstinent for five to six years, and 15 for four to five years. The rest have been abstinent from one to three years.

The over-all percentage of abstainers among the 245 patients is 51.02. These statistics purposely do not exclude patients who combined alcohol with drug addiction; patients who accepted the treatment not quite voluntarily, but under certain pressure from employers or their families; and patients whose chance for rehabilitation was impaired by factors beyond those stemming from alcohol addiction, such as poor working history, lack of trade or profession, criminal background or an occupation that exposes them continuously to alcoholic beverages, such as package-store owners, bartenders, butlers and businessmen who have to entertain.

Psychotherapeutic Aspects and Mechanisms

To consider the conditioned-reflex treatment a mere physiologic or drug therapy would be tantamount to considering only one of its aspects. Like any other physiologic or drug therapy, only even more so, the conditioned-reflex therapy includes a considerable amount of dynamic psychotherapy. As pointed out elsewhere[10] and in the opinion of other authors,* alcoholic patients often suffer from feelings of guilt and inferiority. The patient undergoing the conditioning against alcohol perceives the repeated exposure to the repulsive sight, smell and taste of alcoholic beverages with subsequent nausea as punishment and purification. This procedure of atoning reduces and eliminates his feelings of guilt. On a more superficial level the patients experience a feeling of heroic accomplishment. This in itself is an excellent counterweight for their feelings of diffidence and inadequacy with all the subsequent self-criticism and self-hatred. Thus, it seems reasonable to consider the conditioned-reflex therapy as a psychosomatic approach to a truly psychosomatic disease.

Summary and Conclusions

The rationale, technic, risks, indications, contraindications, efficacy and psychotherapeutic aspects of the conditioned-reflex treatment as applied to 282 patients are discussed.

A new conception of the autonomous character of alcohol addiction in relation to the underlying neurosis is offered. Psychotherapeutic mechanisms involved in the conditioned reflex therapy are pointed out.

*Bird[11] states, "The alcoholic who always feels terribly guilty whether he admits it or not, often feels a need to be punished and being punished . . . may lessen his guilt. . . ."

The therapeutic efficiency of the method available at the Washingtonian Hospital, the only American hospital specializing in the treatment of alcohol addiction, is considered very encouraging.

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THE MANAGEMENT OF ABNORMAL UTERINE BLEEDING*

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EXCEPT for the stain of newborn females and the normal menstruation of constitutional precocity, all the rare cases of uterine bleeding during the period of childhood and preadolescence are but one manifestation of the precocious puberty associated with the following unusual conditions: certain cases of midbrain damage, Albright's disease, exceptional cases of tumor of the adrenal cortex, granulosa-cell tumor of the ovary and, very exceptionally, chorioncarcinomatous teratoma of the ovary. The observation of premature growth and development, then, is the signal for immediate investigation and possible operation. Uterine bleeding after the establishment of the menopause is due most often to intrauterine or ovarian neoplasms, or both, rarely to cancer or sarcoma in the myometrium or to tubal cancer and very rarely to intrinsic vascular disease in the uterus. Between the menarche and the menopause the definite causes of abnormal uterine bleeding are intrauterine tumors and infections, pathologic pregnancy, both intrauterine and extrauterine, retained products of gestation, submucous fibroids, some estrogenic tumors of the ovary, diseases impairing the ability of the circulating blood to clot, and ovarian dysfunction. Placental dysfunction is, of course, involved in the bleeding of pathologic pregnancy. Less clear-cut causes during this span of life are myometrial and subserous tumors, pelvic inflammations, endometriosis, retroversion of the uterus, nonestrogenic tumors of the ovary and uterine fibrosis, since these entities are often present without any abnormality of flow.

It is quite apparent that all the conditions listed — and the list is essentially complete — are, with the exception of infections, not the primary causes of abnormal uterine bleeding. Nor are they the ultimate causes. They are intermediate causes whose primary etiologies are still unknown. As a result of the action of one or more of these intermediate causes, the ultimate factors, chemical and mechanical, that actually rupture blood vessels within the uterus come into play in an abnormal way.

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Management

According to the indications of present knowledge most, if not all, of the complications of pregnancy and the uterine bleedings that sooner or later accompany them are due to placental dysfunction. Because of ignorance concerning primary etiologies, the assumption has been made for years that any disease or disorder anywhere in the body may somehow lead to placental dysfunction. The improvements from better prenatal study and care have justified this assumption. Also because of ignorance concerning specific primary etiologies, it is assumed that any disease or disorder may be an etiologic factor and as such may make ovarian dysfunction a cause of abnormal flowing in the nonpregnant woman, in addition to, or in the absence of, any of the causes listed above. This is the reason for including in the long-range management of abnormal uterine bleeding the study and treatment of the whole patient, even though the beneficial effects may not become at once apparent. Especial and immediate attention is, of course, directed not only to the uterus and adnexa but also to the vulva, vestibule, urethra, vagina and cervix for sources of bleeding. Some women are, understandably, still averse to being examined while flowing. Tragic delays too often result. Their objection is easily overcome when the dangers of delaying the diagnosis and prescribing medication without a diagnosis are explained.

Since it would be futile in a presentation of this sort to attempt a discussion of pathological physiol-

ogy, diagnosis and treatment in relation to all the conditions concerned in abnormal uterine bleeding, a few points under the headings of surgery, radiation and the use of hormones are considered.

Surgery

During the early teens operation is practically never necessary, in either the diagnosis or the treatment of this complaint, which is usually due to ovarian dysfunction of undeterminable cause and responds to the progesterone therapy described below. Some of these young women will have recurrent ovarian dysfunction that can be controlled by progesterone and finally ceases developing. Occasionally, however, one of them continues to have recurrent dysfunctional flowing, and cancer of the endometrium will be found during the twenties or early thirties. Drs. Arthur T. Hertig and Sheldon C. Sommers will soon report 16 such patients whose endometrial hyperplasia became malignant. The patient with persistently recurring dysfunctional bleeding, then, requires particular attention in the matter of follow-up study and endometrial biopsy.

From the age of eighteen on, surgical diagnostic and therapeutic procedures are, of course, increasingly indicated for a great variety of situations of which abnormal uterine bleeding is a sign. This brings me to an aspect of conservative pelvic surgery concerning which I have a strong conviction. All gynecologists have the relatively frequent experience of seeing patients with this complaint who have had previous operations consisting of the excision of both tubes or bilateral tubal ligation, with or without ovarian surgery. These women are usually over thirty-five years old. A uterus capable of only one function, menstruation, yet still capable of being the source of serious or very serious trouble has been conserved. At the Free Hospital for Women 35 patients with cancer of the cervix and 6 with endometrial cancer have had these operations. In addition, 60 to 100 women with bleeding associated with fibroids, chronic pelvic inflammation, polyps and ovarian-endometrial dysfunction who have had these operations are treated each year. The operations had been performed with the mistaken idea, which was due to earlier teachings, that menstruation must be important for health, even in the absence of the ability to conceive. There is no evidence, however, that menstruation has any physiologic value except in relation to fertility. On the contrary, there is ample evidence of its being indeed "the curse." My own conclusion from available knowledge is that it is an expression in the nonpregnant woman of a process that must be very important in the physiology of pregnancy. This process is decidual necrosis, which, according to Dr. Hertig, is a constant feature of human gestation. And certainly amenorrhea in itself is in no way ever harmful. Therefore, it is my firm conviction, and I submit it for serious consideration, that when operations involving sterilization are required, the continued health of these patients is more certainly assured by the removal of the uterus. This prophylaxis eliminates not only menstruation with all its attendant unpleasantness, including premenstrual tension, which is so common to all ages, especially after thirty-five, but also the potential source of tumors, benign and malignant. In retrospect it would have been life saving for many women. It almost completely eliminates soreness of the breasts, and fibrocystic changes in the breasts may disappear after it. I am advocating hysterectomy only in this limited group of patients and not the removal of any ovarian tissue except as indicated in the individual case. When normal ovaries are conserved, menopausal symptoms do not occur prematurely. There are only three exceptions to my proposal. One is that some women, though none in my experience, consider uterine bleeding an indispensable manifestation of their femininity. Another is tubal interruption at the time of cesarean section. The third is when serious systemic illness requires limiting the amount of pelvic surgery to the necessary minimum. In connection with the question whether the hysterectomy should be complete or supracervical, I simply state that, in addition to those whose cancers of the cervix are missed at the time of the incomplete operation, at least 1 of every 100 women so treated will develop this disease some time later. Moreover, 75 per cent of patients with cancer of the cervical stump die of the disease.

After the establishment of the menopause any bleeding from the uterine cavity indicates the presence of a surgical condition. There is no place for the use of hormones in the treatment of postmenopausal uterine bleeding. The condition may be nothing more than an endometrial polyp, which is likely to be found with the placental forceps or a clamp if missed by the curet. A palpable ovary in a postmenopausal patient is always pathologic. Even when no ovarian enlargement can be felt, the finding of hyperplastic endometrium signifies neoplastic ovarian activity. This may be benign but is always potentially malignant, as is the endometrium stimulated by it.

Radiation

The majority of women sterilized by radiation for abnormal bleeding associated with benign conditions, such as ovarian dysfunction and fibroids that are not submucous, get along very satisfactorily so far as later serious or disturbing pelvic troubles are concerned. That radiation is known to provide no immunity to the later development of genital cancer is no contraindication to its employment, for cancer might have developed anyway. On the other hand, according to recent studies, irradiation itself is probably carcinogenic in the susceptible woman. On occasion, a granulosa-cell tumor, thecoma or "thecomatosis" of the ovary appears to have its

etiology in previous irradiation. Also on occasion, atresia of the upper vagina or cervix from this treatment may prevent malignant growths at higher levels from manifesting themselves until too late. In other words, enough patients do have pelvic trouble sooner or later, even up to thirty years, after radiation for benign conditions to make one wish that the original therapy had been surgical or had consisted of temporizing with medical management of the bleeding until ovarian function had become adjusted. Therefore, in general, it seems better to treat fibroids surgically, at the same time avoiding unnecessary castration in younger women. Similarly, it seems better in general to omit radiation for dysfunctional uterine bleeding and, instead, to employ surgery in selected cases and hormones in the others. By selected cases I refer to quite a few women between the age of thirty-five and the menopause who have dysfunctional bleeding, and often premenstrual tension as well, and also prolapse and vaginal relaxation with symptoms therefrom. Many of these are best treated by vaginal, or complete abdominal, hysterectomy without removal of the ovaries, along with reconstruction of the vagina. In the absence of the uterus, simple ovarian dysfunction is harmless, causing little or nothing in the way of symptoms and no signs.

Hormones

Of the available hormones, progesterone and estrogen can be counted upon for predictable, immediate results in the control and regulation of dysfunctional uterine bleeding. Of the various ways of administering these ovarian hormones, I have found the following most effective:

For the patient who has been flowing more than seven days, even for months, at the time the diagnosis of dysfunctional uterine bleeding is made 25 mg. of progesterone is injected intragluteally daily for five days during which the flow will slacken or cease. Two to four days after the last injection of this progesterone series a menstruation, often profuse, will ensue, ending in less than six days. The patient should be warned that the induced menstruation is the necessary evil of this efficient treatment. Normal cycles are likely to follow, for a time at least, but to make more certain of this result it is well to repeat the progesterone series at least once, starting eighteen to twenty-one days from the onset of the induced menstruation. Should irregular bleeding persist between progesterone-induced periods it is certain that some pathologic condition besides an abnormally functioning endometrium is inside the uterus. In other words, the failure of progesterone to be immediately therapeutic, when given as described, points to an incorrect diagnosis and the necessity of investigation under anesthesia at once.

For the patient whose cycles are of normal length but whose bleeding is profuse, or continues up to eight days, and who often has premenstrual staining as well, the simplest therapy is the oral administration of estrogen starting with the onset, or during the first two days, of the period. Estrone sulfate, in divided doses totaling 10 mg. daily, is taken for twenty-five days. To reduce expense, stilbestrol in daily doses of 5 mg., 10 mg. or even 25 mg. may be taken, on retiring, instead of estrone sulfate. Both of them may cause malaise in some women; in others a sense of well being is produced. The occurrence of bleeding between the sixth day and the end of estrogen treatment indicates the presence of some undiagnosed condition within the uterus. Two to six days after the cessation of medication uterine bleeding will begin. Though not profuse, it occasionally lasts up to eight days. Thereafter, normal catamenia may or may not ensue. Should excessive flow again appear early in a cycle, the estrogen treatment may be started at once and continued again for twenty-five days.

For this type of abnormal bleeding the progesterone series also has a place. If elected, it should be started between the eighteenth and twenty-first days of the cycle. Although in some women the ensuing catamenia may be profuse, it will not last so long. Moreover, there is a greater chance that normal catamenia will follow than after the estrogen treatment.

For the woman whose cycles are disturbingly shortened, whether or not her bleeding is profuse or prolonged, the progesterone series is begun eight days before the expected onset of a period. Or the estrogen treatment is given beginning at the start of flow. Here again, uninterrupted bleeding during estrogen treatment or following a post-progesterone menstruation is indicative of an incomplete diagnosis.

Conclusion

The management of abnormal uterine bleeding is fundamentally similar to the management of any other sign or symptom. It involves the diagnosis and treatment of definite and possible causes, the direct treatment of the complaint in the absence of determinable causes, and the therapy, so far as possible, of all other discoverable abnormalities. I am reminded of the illustrious statement by Dr. Francis W. Peabody that "The secret of the care of the patient lies in caring for the patient." I take the liberty of paraphrasing it as follows: the secret of the care of the patient lies in taking care of the *whole* patient.

MEDICAL PROGRESS

RESUSCITATION (Concluded)*

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ASPHYXIA NEONATORUM

Asphyxia neonatorum is the most frequent emergency requiring resuscitation that is encountered in the delivery room. It is characterized by the absence of spontaneous effective respiration. The mechanism of the development of this type of respiratory arrest differs from those classified in the previous section, but the resultant pathological physiology has much in common with them.

The difference between asphyxia neonatorum and cardiorespiratory arrest is that in the latter both respiration and circulation cease and must be maintained artificially, whereas in asphyxia neonatorum, it is rare for the heart to stop beating and it is only the respiratory arrest that requires artificial correction. That this basic difference is generally accepted is well substantiated by the fact that artificial respiration in relation to asphyxia of the newborn is extensively discussed in the literature, while mention of cardiac resuscitation of the newborn is conspicuously rare. It is obvious that the newborn infant who has both respiratory arrest and cardiac arrest has declined to a state that is irreversible. As in all other cardiorespiratory accidents, the indispensable primary principle in the treatment of asphyxia neonatorum is the urgent necessity of delivering oxygen to the tissues before anoxic changes become irreversible. The most prominent anoxic manifestations are cardiac arrest and damage to the brain.[97]

Pathological Physiology

The pathological changes in various organs contingent upon the anoxia in asphyxia neonatorum are typified by congestion of blood vessels, interstitial edema, diapedesis of blood cells, hemorrhages and necrosis of tissues.[98] In cases in which anoxia does not advance to the point of cardiac arrest the greatest danger is damage to the brain. Russ and Strong[99] indicate that prolongation of anoxia for more than two minutes after delivery of an infant will cause serious cerebral changes. Numerous reports and experiments prove that brain damage can occur despite successful resuscitation and can result in crippling sequelae such as mental inferiority, diminution of ability to learn and mental dullness.[100, 101] Studies of groups of children who had suffered varying degrees of asphyxia neonatorum revealed a high incidence of abnormal cerebral function, low intelligent quotients, retardation in later life and markedly affected behavior patterns often to a point incompatible with normal living; 26 per cent of the children were morons, imbeciles or idiots.[102-104] These observations emphatically indicate that the major damage to the brain of the newborn infant from anoxia is manifested in later developmental abnormalities.

The outstanding pathological lesion at autopsy in cases of asphyxia neonatorum is the complete atelectasis of the lungs, which are airless, without crepitance, and are a compact solid viscus having a fleshy parenchyma.[100, 105, 106] Partial atelectasis may exist for long periods after respiration begins.[107]

The alterations in blood chemistry in asphyxia neonatorum are not discussed; the reader is referred to the respective section of the collective review on this subject written by Little and Tovell.[100]

Etiology

Little and Tovell[100, 108] point out in two excellent reviews on the subject of asphyxia neonatorum that the complete syndrome is usually the result of a combination of several of the numerous etiologic factors rather than any one factor in itself. They catalog the etiologic elements in three groups: those pertaining to the mother; those pertaining to the products of conception; and those pertaining to the labor and delivery.

There is a significant increase in the incidence of asphyxia of the newborn when the mother's age exceeds forty years,[99, 109] when the mother is a primipara or multipara after the eighth pregnancy,[110, 111] and when the mother's health has been adversely influenced by cardiac disease, pulmonary disease, genitourinary infection, gastrointestinal disorders, metabolic disturbances and toxemia of pregnancy.[111-115]

Abnormalities of the products of conception related to low viability of the germ plasm, immaturity of the fetus, congenital defects such as malformation of the respiratory and circulatory systems, and congenital debilities such as syphilis and erythroblastosis fetalis adversely affect the inci-

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dence of neonatal asphyxia.[107, 116-119] Furthermore, the role of unfavorable position of the fetus in the uterus — particularly breech, transverse and occiput posterior presentations — is of appreciable significance.

The factors pertaining to the labor and delivery that are regarded as of tremendous importance by Little and Tovell in unfavorably influencing the occurrence of asphyxia neonatorum are as follows: duration and type of labor — long, dry labor or long difficult labor associated with cephalopelvic disproportion[113, 114, 120]; induction of labor with drugs such as quinine and Pituitrin[111, 112, 120, 121]; complications of labor — infarction of the placenta, low insertion of the placenta, placenta praevia and premature separation of the placenta, anoxia to the fetus originating in impaired circulation in the cord and anoxia to the fetus of uterine origin[99, 113, 115, 122, 123]; type of delivery — version and extraction, high forceps, breech extraction, mid forceps, cesarean section and low forceps without episiotomy[110, 114, 116, 122, 124]; and analgesic drugs and anesthetic agents and methods.[108, 113]

In a series of 143 infants who died in the neonatal period from asphyxia and atelectasis, Roberts[125] found the close relation between intracranial damage coincident to difficult labor and this type of death very prominent; 55 of these infants evidenced intracranial damage. Confirmation of this observation is contributed by Russ and Strong,[126, 127] who also call attention to the importance of debris in the newborn infant's trachea as a cause of respiratory difficulty, particularly when delivery has been accomplished by cesarean section.

Diagnosis and Classification

The diagnosis of asphyxia neonatorum is made by the simple observation that respiration is absent. Ascertaining the concomitant degree of anoxia is not so simple and is of major importance. Many classifications have been recorded to describe the conditions produced by progressing oxygen deficiency.[128-132] The following classification offered by Flagg,[133] in which physical findings are the basis for diagnosis, is the one generally accepted and is the most practical from the therapeutic point of view:

1. *Stage of Depression*: baby does not breathe well; tendency to duskiness and recurring cyanosis; respiration free, but slow and irregular.

2. *Stage of Spasticity*: irregular, gasping, or shallow respiration occurring at long intervals; marked cyanosis of mucous membrane with blotching of skin or general pallor; the baby's gums close over the gloved fingertip; reflex reaction to suction of the pharynx, such as movement of facial muscles or extremities; if pharynx is exposed, pharyngeal reflex is sluggish or active and the glottic reflex is active.

3. *Stage of Flaccidity*: respiration occurs at long intervals or cannot be demonstrated; cyanosis or pallor; complete flaccidity of musculature, all muscle tone gone, jaw completely relaxed; no resistance to suction or exposure of the pharynx; fluid is found in hypopharynx; apex beat may or may not be demonstrable.

Prophylaxis

Since many of the etiologic factors capable of abetting the occurrence of asphyxia neonatorum are to some extent under the control of the physician much can be done in the way of preventive measures to reduce the incidence of this condition. Factors that are partially controlled by the physician are listed as follows by Little and Tovell[108]: the health of the mother, congenital disease of the fetus, presentation and position, and the duration and type of labor and delivery. The last of these has further been highlighted by an analysis by Russ and Strong[99] of more than 1000 cases of asphyxia neonatorum enabling them to draw the conclusion that the prolongation of labor in association with a traumatic type of delivery is by far the most notable single cause. The emphasis upon the importance of conscientious and intelligent observation during the conduct of labor and the election of the safest and most suitable methods of delivery as vital prophylactic measures in asphyxia of the newborn is apparent.

Within the complete control of the physician are the induction of labor and the use of analgesics and anesthetics. The latter is important enough and controversial enough to demand some elaboration. Little and Tovell[108] have made a comprehensive study of this subject that enables them to conclude that there is a close causal relation between an increase in asphyxiated infants at birth and the use of analgesic and anesthetic drugs, in that every one of them may increase the incidence of this complication. They endorse and commend the approach of Grantly Dick Read to the problem of relief of pain in childbirth. This method is one in which a mental prophylaxis against fear is initiated in the expectant mother and renders the use of drugs unnecessary in the majority of cases.[134, 135] Read's[136, 137] practices have been gaining widespread recognition during recent years.

Though sounding a warning, Little and Tovell[108] do not condemn modern analgesia and anesthesia, "for the fault lies not so much in the drugs but in their methods of application." They signify that the following pharmacologic principles must be scrupulously adhered to when analgesics and anesthetics are administered: "each patient must be evaluated and treated on an individual basis; the dosage of the drugs administered must be the minimal effective dose; the physician must be in constant attendance to evaluate the effects of the agents on the woman in labor; cognizance must be taken of the presence of other factors besides those of analgesia and anesthesia that may tend to produce asphyxia neonatorum, and the use of

analgesics and anesthetics must be modified accordingly."

Treatment

In the treatment of asphyxia neonatorum there are two objectives: to *deliver oxygen to the tissues* — as in any case of cardiorespiratory arrest, the salvaging of life and the avoidance of permanent brain damage will depend upon the successful execution of this principle by ventilation of the lungs; and to *protect the infant from harmful influences* — by institution of measures that safeguard normal physiology.

Whereas the aims in the treatment of cardiorespiratory arrest are achieved one after the other, in the treatment of asphyxia neonatorum both propositions must be carried out simultaneously.

Since asphyxia neonatorum is not complicated by cardiac arrest there is no need for the maintenance of circulation by cardiac massage.

The first aim of resuscitation of the newborn is delivery of oxygen to the alveoli of the lungs by either stimulation of spontaneous respiration or artificial respiration.

Stimulation of spontaneous respiration. It must be borne in mind that this approach is justified only in the first stage of asphyxia, that of depression, in which the baby does not breathe well; respiration is slow and irregular. Gentle cutaneous friction, passive movements of the extremities and catheter aspiration of the nose, mouth, and pharynx are the acceptable procedures for this purpose.[115, 138-141]

Artificial respiration. If the infant does not breathe within thirty seconds of severing of the cord, artificial respiration must be instituted regardless of the stage of asphyxia.[99, 115] The most efficient method of applying artificial respiration to the newborn appears to be that performed by the employment of the Kreiselman resuscitator.[142-146] This mechanical resuscitator supplies an intermittent flow of oxygen under a controllable positive pressure, which may never exceed 15 or 16 mm. of mercury. Oxygen is administered thirteen to fifteen times a minute, two or three seconds being allowed for inflation and two seconds for passive deflation; a positive pressure of 12 mm. of mercury is applied at the outset for inflation of the lungs, and this may be increased to 14 or 15 mm. In the newborn this amount of positive pressure will not cause the chest to rise in the inspiratory phase because the lungs expand in a patchy distribution and it may take a long time for them to be thoroughly inflated. As Kreiselman[147] avers, the machine should be at hand in perfect working order for every delivery, and personnel expert in its use should be present.

If these conditions cannot be fulfilled and a simpler, immediately available means of administering artificial respiration must be resorted to, mouth-to-mouth insufflation is considered the next choice.[78, 107, 142, 148-151]

Disadvantages associated with this method are that it does not supply 100 per cent oxygen, there is the danger of the creation of excessive intrapulmonic pressure, which may cause fatal emphysema or pneumothorax, there is the possibility of overdistending the stomach and rupturing it, and the procedure may lead to infection of the infant or of the operator.[152-157]

Other means of artificial respiration employing resuscitators of the "suck and blow" type have been commended and condemned.[120, 129, 158-164] Infant respirators of the Drinker type seem to have little practical value.[165-169]

The dangers of excessive positive pressure mentioned above are present with all types of mechanical resuscitators, but they appear to be least likely with the Kreiselman apparatus, which provides the most adaptable means of positive pressure control.[170] Finally, manual methods of artificial respiration in asphyxia neonatorum are observed to have no physiologic basis and are therefore of no value in the resuscitation of asphyxia of the newborn.[153, 157, 171-173]

The establishment and maintenance of a free air passage should be considered a part of the technic of artificial respiration. It is obvious that, without a free airway, oxygen cannot reach the alveoli of the lung. Gentle catheter aspiration of the nares, mouth, pharynx and, when necessary, the trachea and upper bronchial tree is advisable to remove aspirated material such as amniotic fluid, meconium and cellular debris, which may be the source of obstruction.[151, 158, 159, 165, 170, 174] Placing the baby in a head-down position helps serve the same purpose of draining material from the air passage; 15 to 30° of Trendelenburg position is considered optimal.[120, 153, 170] In cases in which asphyxia has advanced to the stage of flaccidity, the collapsed glottic structures will produce obstruction of the airway. To obviate this obstruction, tracheal intubation is mandatory.[129, 133, 139-141, 175-178] The need for considerable skill in performing this procedure without trauma to the larynx is emphasized.[101, 149, 174]

The manipulations necessary to the establishment and maintenance of a clear airway are performed repeatedly as needed in conjunction with artificial respiration but in such a manner that artificial respiration is interrupted for only very brief periods. Performance of the initial aspiration of the upper respiratory tract is advisable the moment the head has been delivered and before the umbilical cord has been clamped.[101, 133]

Formerly, the use of carbon dioxide was advocated as a stimulant to respiration in the resuscitation of asphyxia neonatorum; at present the use of carbon dioxide is considered useless or even harmful.[179-183]

The status of drugs in the treatment of asphyxia neonatorum is identical with that of carbon dioxide or with that of drugs in the treatment of cardiorespiratory arrest; epinephrine, alpha lobeline, Pituitrin, camphor, coramine, picrotoxin, Metrazol, caffeine and strychnine have been proposed for consideration or have enjoyed the commendation of a number of observers.[156, 157, 174] More recently, the consensus is that they are likely to do more harm than good.[160, 162, 173]

The second aim of resuscitation of the newborn infant — that of maintaining normal physiology — is best furthered by scrupulous adherence to two simple principles. The first of these is the minimal handling of the infant to reduce the possibilities of shock, visceral lacerations and cerebral hemorrhage. There appears to be little justification for such "archaic methods of man-handling" as the Schultze giant swing, hot and cold tubbing, sprinkling the skin with ether, vigorous spanking, pummeling, dilating the anal sphincter and penile dorsal slit.[100, 120, 172, 184] Suspension by the feet to promote drainage of the respiratory tract, as formerly advocated, may aggravate the danger of cerebral hemorrhage. This suspended position is best avoided, and the optimal position of 15 to 30° Trendelenburg, as indicated above in the discussion of maintenance of a free air passage, should be utilized.

The second principle is immediate warmth. The importance of the retention of normal body temperature has been stressed.[99, 100, 147] The practical importance of this measure has not been affected by theoretical objections.[185]

These essentials must be observed from the moment of birth throughout the period in which the newborn infant requires resuscitation.

Russ and Strong[99] believe that "the after-care of the newborn resuscitated baby is of equal importance to that of the resuscitation itself." This care includes preservation of oxygen physiology by inhalational therapy, close observation, placement in an incubator, withholding of feeding and the administration of a stimulant if necessary.[99, 115, 126, 127]

* * *

The neonatal period is the most hazardous in life; here the mortality rate exceeds that of any other time, and the danger of permanent central-nervous-system damage is ever present.[147] The persistent use of many faulty practices in the treatment of neonatal asphyxia may be an important factor contributing to fetal and neonatal mortality rates, which have improved but little during the past century.[107, 133]

Although, in practice, resuscitation of the asphyxiated newborn infant remains primarily the province of the obstetrician,[125] in the words of Little and Tovell[108]: "The anesthesiologist has come to join the obstetrician in being responsible not only for the safe and painless labor of the mother but, also, for the safe deliverance of her infant, including, when necessary, the resuscitation of that infant."

Asphyxial Accidents Outside the Operating Room and the Delivery Room

The number of causes that may lead to asphyxial accidents in places other than the operating and delivery rooms is large and varied. Of these, the most important are inhalation of gases such as carbon monoxide, — illuminating gas and engine exhaust, — industrial gases — chemical, mine, refrigerants, smoke and chemical fumes; drowning; electrocution; drug poisoning from hypnotics, narcotics, sedatives and alcohol; and mechanical obstruction to respiration from smothering, strangulation, compression of the chest and choking — aspiration of foreign material and disease in the respiratory tract such as infection, tumor or allergy.[113, 186, 187]

In any of these conditions interruption of the oxygenation of the tissues is induced by either interruption of pulmonary ventilation — such as that which occurs in drug poisoning and electrocution, when the respiratory center is paralyzed, or as in drowning and mechanical obstructions of air passages, when effective ventilation becomes impossible; or interference with the oxygen-carrying power of the blood — as in carbon monoxide or nitrite poisoning; or finally arrest of the capacity of cells for utilizing oxygen (histotoxic anoxia) — as in cyanide poisoning.[107]

Although not of such vital significance as the lack of oxygen in asphyxial conditions, the retention of carbon dioxide in the blood contributes appreciably to the resultant asphyxial syndrome.[188, 189]

When electrocution is the etiologic factor in an asphyxial accident, the respiratory arrest may be complicated by concurrent cardiac arrest.[133]

The location of asphyxial accidents has a notable bearing on their outcome.[190] Obviously, the facilities available for resuscitative therapy are more immediately accessible in the emergency room of the hospital, the first-aid station or the doctor's office than in the home, at the roadside or river bank or in the field. Of equal significance is the personnel immediately available for initiation of life-saving measures; there can be no comparison between the effectiveness of the doctor or adequately trained first-aid technician and that of the casual passerby or inadequately informed lay person.

The classification of the stages of asphyxia given above in the section on asphyxia neonatorum is applicable to most of these asphyxial accidents. In the majority the initial stage is characterized by depression, which is followed by a period of struggle associated with spasticity and, finally, the third stage, in which there is complete flaccidity.[128, 133]

A discussion of the pathological physiology, symptomatology, prophylaxis and special problems related to any one of these accidents, although fundamentally important to the physician, has been

omitted from this presentation. Most of this information may be obtained from Flagg's book on resuscitation.[133]

Treatment

In the treatment of accidents of asphyxiation, it is imperative that two goals be attained: immediate delivery of oxygen to the alveoli of the lungs by artificial respiration; and support to the circulation, which is failing from anoxia.

Artificial respiration. In accentuating the great importance of the time element in resuscitation, Comroe and Dripps[188] list the following basic principles that must be adhered to regardless of the nature or place of the accident: "The most immediately available method must be employed instantly" and "as soon as possible the most efficient method of artificial respiration should replace the emergency measure."

If, when a victim of an asphyxial accident is encountered, there are no facilities at hand for providing resuscitation, which is most often the case, the only method immediately available is manual artificial respiration.[69, 128, 191] Of the several methods the generally approved technic is that of Schaefer, which employs rhythmic compression of the lower thorax with the patient in the prone position.[34, 192, 193]

The manual methods of artificial respiration, even though properly executed, do not provide sufficient respiratory exchange and should not be regarded as definitive but only as a temporary emergency measure.[188, 194-197]

The means of providing efficient artificial respiration to replace the emergency manual procedure include the following:

Rhythmic inflation of the lungs by use of a mechanical apparatus. Of these the simple and small bellows-type device introduced by Kreiselman appears to offer definite advantages in that it accomplishes adequate pulmonary ventilation with air or oxygen, when it is available; it is compact, inexpensive and easily portable.[143] Other more elaborate machines for performing artificial respiration are obtainable on the market. Among these are the E and J, the Emerson, B-K, Davis, and H and H inhalators and resuscitators.[129, 133, 198] They supply 100 per cent oxygen or a mixture of oxygen and carbon dioxide by either alternating positive or negative pressure from 15 to 25 mm. of mercury. These machines are mechanically accurate but not quite so easily transportable.

The tilting method of Eve. This method utilizes the tilting of the patient 45° in the head-up position (inspiratory phase), followed by a sharp reversal to 45° in feet-up position (expiratory phase). Respiratory exchange is produced by movements of the diaphragm in response to ascent and descent of the abdominal viscera with the sudden changes in position. The respiratory exchange afforded is better than that with manual methods, and although this means of artificial respiration is highly recommended, its efficiency does not approximate that of rhythmic inflation of the lungs by apparatus employing positive pressure. Further limitations are difficulties encountered in transporting or improvising the necessary apparatus. Eve's tilting method does contribute two features of value irrespective of its utility for artificial respiration. These are a beneficial massaging effect on the heart and the facilitation of drainage from the respiratory tract when it is used in the treatment of a victim of drowning.[78, 188, 199]

Insufflation of oxygen with endotracheal intubation. Insufflation of oxygen without respiratory excursions of the chest can provide oxygenation and might be employed in the treatment of asphyxia; however, it should not be used for more than a few minutes without the addition of rhythmic manual compression of the chest because the accumulation of narcotic concentrations of carbon dioxide will occur.[188, 200-202]

The establishment and maintenance of an unobstructed airway is a prerequisite of artificial respiration. None of the methods of performing artificial respiration will be effective without patency of the air passage. It is because automatic machines for supplying artificial respiration are so often employed with disregard to respiratory obstruction that they have been generally considered both hazardous and unscientific.[133] The same observation is applicable to other methods of artificial respiration.

One of the most frequent causes of interference with the free passage of air is an abnormal position of the pharyngeal structures as represented by the backward displacement of the tongue, which is more prone to occur in the supine position than when the victim is face down.[195] Regardless of the type of artificial respiration employed, the operator must be constantly on the alert for this possibility.[133, 181] Proper support of the jaw, pulling the tongue forward and insertion of nasal or oral "airways" are simple measures and may contribute to overcoming the difficulty; on the other hand, they may be inadequate.[112, 116] The passage of an endotracheal tube, which requires experience and often a good deal of time, assures a patent respiratory passage and is urged by Flagg for all patients who have declined to the stage of flaccidity.[133, 203]

Other causes of respiratory obstruction are occlusion by some foreign body or by a pathologic deformity of the respiratory tract. These may be the initial causes of asphyxial accidents as illustrated by the example of a victim of choking.[107, 133, 186] In the event of a pathologic deformity or inhalation of a foreign body, when simple measures such as suspending the victim head down and finger exploration of the throat have failed to

dislodge the obstructing material, emergency tracheotomy or intubation will be required.[133, 181]

Several factors such as the nature of the obstruction, the stage of asphyxia, the available facilities and familiarity with these technics determine whether tracheotomy or endotracheal intubation should be resorted to. Gross deformity of the glottis may render intubation impossible. The victim in the stage of spasticity is unsuited for intubation.[133] Patients in the first or second stage of asphyxia who have an appreciable respiratory exchange irrespective of the nature of the obstruction may be given oxygen with maximum available intermittent positive pressure synchronized to the patient's respiration during transportation to the nearest hospital, where immediate tracheotomy, laryngoscopy, bronchoscopy or intubation may be performed.[133, 181, 204-206]

After tracheotomy, if the resuscitating apparatus can be attached to the tracheotomy-tube opening so as to be airtight, oxygen under intermittent positive pressure should be administered. If it is not possible to supply such an airtight system, a constant flow of oxygen should be insufflated through the tracheotomy opening while manual artificial respiration is simultaneously applied.[107, 133, 181, 204]

The causes of respiratory obstruction enumerated above may be further aggravated by aspiration of regurgitated gastric contents or other fluids and by the presence of excessive secretions. Brief and repeated catheter suction and postural drainage of the patient to remove these products should be utilized as necessary.[107, 133, 181]

The gas used for artificial respiration should always be 100 per cent oxygen except in carbon monoxide poisoning.[205-208] It has been demonstrated that with the addition of 5 to 10 per cent of carbon dioxide to the inhaled atmosphere, the elimination of carbon monoxide will be faster and the availability of oxygen to the tissues will be increased.[107, 209-211]

The second aim of resuscitation in asphyxial accidents — that of providing support to the failing circulation — includes measures to combat shock and stimulate heart function.[212-214]

If facilities permit, fluid therapy should be administered intravenously, and measures by which the venous return to the heart can be increased, such as the Trendelenburg position, raising the legs to the vertical position ("autogenous transfusion") and application of tourniquet to the extremities, should be utilized.[215-219] Normal body temperature should be maintained, but care must be taken not to overheat the patient.[220]

Employment of drugs that stimulate circulation such as epinephrine, ephedrine and related amines should be resorted to only if complete oxygenation has been established.[215, 218, 221]

During the aftercare when the patient has regained spontaneous respiration, further inhalation and fluid therapy, supervision of a free respiratory exchange, attention to bladder and bowel functions and the maintenance of body temperature are in the realm of general nursing care but are essential components of thorough treatment.

* * *

A trend that had developed over the past twenty years has led to an undesirable situation regarding asphyxial accidents. This situation is characterized by overzealous activities of lay rescue squads and at the same time a lack of professional interest in problems of resuscitation on the part of the physician. Insufficient essential knowledge of the anatomy of the respiratory tract, physiology of respiration, pneumatology, physiology of anoxia, pathological physiology and diagnosis of asphyxia is an obvious limitation to the capabilities of the lay rescuer. That this limitation is often not appreciated is evidenced by the calls to lay rescue squads that originate even from the operating and delivery rooms. The attitude of the medical profession frequently implies that the treatment proffered by the mechanical performance of the lay squad, aided by the inhalator, leaves nothing more to be desired.[133]

The resolution by the American Medical Association to encourage instruction of medical students and postgraduates in pneumatology and in the treatment of asphyxial accidents, the activities of the Society for the Prevention of Asphyxial Deaths, Incorporated, and the inclusion of resuscitation as a basic subject in the specialty of anesthesiology, along with other efforts on the part of the medical profession, are laudable measures for the improvement of the situation.[222, 223] It is hoped that in the future, in the words of Flagg[133]: "When the average physician looking upon impending asphyxial death is shocked into a realization that here and now is the supreme test of his life-saving skill as a physician, resuscitation will cease to be relegated to the care of those lay groups whose services have been and continue to be a bridge to span the period between helplessness and adequate medical care."

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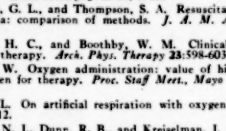
CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 35371

PRESENTATION OF CASE

A forty-eight-year-old truck driver was admitted to the hospital because of severe hematemesis.

Five months before admission, while in a distant city, the patient suffered a sudden severe hematemesis. Several "liver-chemistry studies" performed at that time were normal, except the prothrombin time, which was 75 per cent of normal. The findings on a gastrointestinal series were somewhat equivocal but suggested esophageal varices, gastritis and "possible ulcer in the first portion of the duodenum." He was given five transfusions, "the last four of which gave him reactions." Jaundice promptly developed, and the icteric index rose to 18 units. Administration of vitamin K failed to improve the prothrombin time. Bleeding stopped, and over the ensuing two weeks the jaundice faded. He lost 15 pounds in weight during the illness, and spent the following three months in convalescence before returning to his truck route. During the convalescent period an additional transfusion was administered to the patient without event. Eight teeth were extracted, after which blood oozed from the gums for what was considered a prolonged period. The gastrointestinal series was repeated, but no abnormalities were discovered. He returned to work and felt well, remaining free of symptoms until the day of admission. While driving his truck he "felt sick" and then suddenly vomited a large amount of blood. During the five hours required to transport him to the hospital, he had five additional episodes of vomiting. He felt weak, nauseated and intensely thirsty but not faint or "sweaty." Since the onset he had had one brown bowel movement.

His mother had died of cancer. His wife had suffered from tuberculosis at the time of their marriage, twenty years before admission, but had been in good health at the time of her husband's illness.

As a young man the patient had drunk large quantities of beer, up to several quarts a day. In recent years he had reduced the intake to a bottle a day. Six months before entry he spontaneously

stopped drinking and "has not touched a drop since."

Physical examination revealed an acutely ill, well developed, well nourished moderately pale man. The skin was hot and dry. There was a single "spidery angioma" on the left upper arm. A dilated venule that "seemed to end abruptly" was found on the posterior pharynx. The chest was clear. The heart was slightly enlarged to the left. The rhythm was regular, and the sounds were hyperactive. A Grade II systolic murmur was heard over the entire precordium and was transmitted to the axillas and neck. The abdomen was nontender and not distended. The liver edge was barely palpable at the liver margin. The spleen was not felt. Peristalsis was diminished. Rectal examination was negative.

The temperature was 102.6°F., the pulse 130 and the respirations 30. The blood pressure was 80 systolic, 50 diastolic.

The hemoglobin ranged from 11 to 12.5 gm. The white-cell count was 17,000, with 78 per cent neutrophils. The platelets were normal morphologically. There was slight erythrocytic hypochromia. The urine specific gravity was 1.025. The sugar test was brown, but intravenous glucose solution was being administered. A stool was brown and gave a + guaiac reaction.

Throughout his short hospital course the patient remained acutely ill, constantly febrile and in a constant state of shock. At intervals of one to four hours he vomited copious quantities of bright-red blood, losing a total of 4500 cc. by hematemesis. Parenteral injection of vitamin K and 6000 cc. of blood were administered during the first twenty-four hours. Attempts at esophageal tamponade were unsuccessful because of vomiting. Large doses of sedatives were given, and a state of semidelirium developed. At the end of twenty-four hours his condition stabilized somewhat. The blood pressure rose to 140 systolic, 70 diastolic, but tachycardia persisted. An emergency barium study of the esophagus was reported as showing "unequivocal varices." Twelve hours later there was a sudden drop in blood pressure to 80 systolic, 60 diastolic. Respiratory and cardiac failure quickly ensued despite the rapid administration of 1000 cc. of blood.

Large amounts of blood welled into the pharynx, and the patient died thirty-six hours after entering the hospital.

Differential Diagnosis

Dr. Myles P. Baker: This is a brief story of massive hematemesis in a forty-eight-year-old man who was brought to the hospital bleeding to death, with a history of a similar but less severe hematemesis five months before, unexplained as to etiology.

The problem facing his physicians, primarily, was to save his life. That involved certain diagnostic procedures, because they had to consider the possibility of bleeding peptic ulcer for which surgical treatment might be necessary — hence, I suppose, the so-called emergency barium study of the esophagus done during the twenty-four hours preceding death. Was that only a fluoroscopic observation, Dr. Mallory?

Dr. Tracy B. Mallory: I cannot be sure.

Dr. Baker: The data regarding the first hematemesis were, I suppose, obtained from the family. I think that one of the critical findings during that first episode of hematemesis was the jaundice. It is noted in the protocol as developing promptly after transfusions, which led to reactions. Reactions following transfusion are generally reported as occurring in approximately 6 per cent of cases, even when all reasonable precautions are taken. Reactions are not usually hemolytic — usually mild, febrile or urticarial. It is well to remember that chill following transfusion does not necessarily mean that hemolysis has taken place. The rule, as far as jaundice is concerned following transfusion, is that it can be expected about twelve hours after transfusion if a hemolytic reaction has taken place; it is a transient affair and is no longer observed after the passage of three or four days, at the most. My impression, then, of this comment that jaundice promptly developed is that jaundice was observed at that time but may have been present for some time before. Often, people recognize jaundice at a given time, but actually it has been there quite a while. Jaundice that took two weeks to fade, I would think, was much more likely due to liver disease. It would be consistent with an episode of jaundice in the course of cirrhosis of the liver. Jaundice in cirrhosis of the liver is statistically common, but it has to be remembered that it is of ominous prognostic significance. Once it appears, it generally does not disappear entirely, as the jaundice appears to have done in this man over his convalescent period of three or four months between hematemeses. I should say that the chances of having jaundice with cirrhosis of the liver, as a result of functional disturbances of the liver cells, and having it disappear would be no more than one chance in five or six — so that my stand that this jaundice was due to liver disease rather than any hemolytic reaction is something of a far cry. But I would prefer it to explaining the jaundice on the basis of hemolytic reaction to blood transfusion.

We have no evidence of any chemical studies to support either explanation for his jaundice. The prothrombin time of 75 per cent of normal is barely below what is found in a good many people when prothrombin times are determined on the wards. Of course, it must be below 20 per cent of normal before one runs into any serious hemorrhagic trouble, and this one finding is rather a weak reed for a diagnosis of cirrhosis of the liver. Could a prolonged prothrombin time be the one abnormal liver-function

test in cirrhosis of the liver? Yes, it could be, but it is uncommon.

The significance of the bleeding from the gums during the period of convalescence is, I think, very dubious. We cannot lay any stress on it. At the time of his first and final admission here one single spider angioma was observed on the left upper abdomen. This may or may not have been of really diagnostic importance. Spider angiomas are found in varying percentages of patients reported with cirrhosis, depending on the interest of the observer and the carefulness of the examination. They have been reported by careful observers in 75 per cent of a series of proved cases of portal cirrhosis. I can recall a case presented here this spring in which a single spider angioma observed by a visiting physician — and not previously recognized as such by others — was associated with proved fatty changes in the liver. In that case it was a very important diagnostic point. Spider angiomas do occur in other diseases — in vitamin B complex deficiency, notably. But the genuine article is usually associated with hepatic disease, and that is usually portal cirrhosis. I am surprised at the height of the hemoglobin figure, and cannot explain it in a patient who was in shock. I suppose it was taken at the time when he had just had a transfusion and had not yet begun to bleed again. I presume, with the roentgenologic observation, that there were unequivocal esophageal varices, that the medical officers in charge of the case expected that at post-mortem examination cirrhosis of the liver would be found. Is it possible to have such an advanced stage of cirrhosis of the liver that esophageal varices are present and detectable by x-ray study and bleed, with normal liver-function tests? It must be the exception to the rule. One roentgenologist who has had a great deal of experience with the demonstration of esophageal varices tells me that although he could not put his finger on an individual case he believes that they must occasionally occur. We do not know what liver-function studies were done five months before admission, and no attempt could be made at this admission for further studies, but it would surely not be unreasonable to assume that bleeding esophageal varices were the cause of this man's death.

What other possibilities might there be? Peptic ulcer is the commonest cause of massive hemorrhage in the upper gastrointestinal tract, accounting for probably 60 to 75 per cent of such cases. We must consider it in any event — if only on the basis that the x-ray examination five months before suggested an acute duodenal ulcer. The association of cirrhosis of the liver and duodenal ulcer has been commented on several times; whether it is more than a coincidence or not is not established. So, even if this man did have unequivocal evidence of esophageal varices just prior to death he still may have been bleeding fatally from a duodenal ulcer. Such an explanation has been advanced under similar circumstances in cases presented here. If this man had cirrhosis of the liver, he may have been bleeding, if not from esophageal varices, from a much engorged mucous membrane in the upper third of the stomach, sometimes found in such cases either in association with, or in the absence of, erosions of varices in the lower end of the esophagus.

It is noted here that the hematemesis was described as "copious quantities of bright-red blood." That might be interpreted as arterial blood; more typical, perhaps, of the bleeding from duodenal ulcer or gastric ulcer than from esophageal varices. On the other hand, it is so characteristic for the patient with bleeding esophageal varices to have blood well up into the pharynx that there may be evidence here on one side as well as the other.

My impression is that this man had cirrhosis of the liver and bleeding esophageal varices. There may have been an associated duodenal ulcer, which was a primary factor in his bleeding; but we have no more than a suspicion for it.

A PHYSICIAN: Did he have an enlarged spleen?

DR. BAKER: Not enlarged, so I should think one had no reason to consider congestive splenomegaly — Banti's disease.

CLINICAL DIAGNOSIS

Ruptured esophageal varices.
Laennec's cirrhosis?

DR. BAKER'S DIAGNOSES

Portal cirrhosis.
Esophageal varices, with massive and fatal hematemesis.
Duodenal ulcer?

ANATOMICAL DIAGNOSES

Portal cirrhosis of liver, alcoholic type.
Esophageal and gastric varices, with ulceration and hemorrhage into gastrointestinal tract.
Gastritis, acute.
Diverticulum, congenital, of duodenum.

PATHOLOGICAL DISCUSSION

DR. MALLORY: Autopsy on this man showed a cirrhotic liver. It was enlarged, very finely granular, tough, pale and evidently fatty. Its gross appearance and the subsequent microscopical findings were characteristic of what we ordinarily call alcoholic cirrhosis of the liver, despite the history of the consumption of nothing stronger than beer, and not even that for the last six months. One can interpret that as one chooses. The man was a truck driver, and a written record of alcoholism might have caused him to lose his job so I do not believe one can take it at its face value. Moreover, truck drivers as a group eat very well, so that malnutrition is very unlikely unless provoked by alcoholism.

I would like to vindicate the outside x-ray findings. This man had large and definite esophageal and gastric varices and also a very severe gastritis, which was hemorrhagic in part. There was a deep crater-like lesion of the duodenum that looked at first glance like a deep penetrating ulcer. In its center was a ridge that proved to be the common bile duct. It was lined by normal mucous membrane and represented a congenital diverticulum. The ampulla of Vater is a common site for such a lesion. On x-ray examination it could readily be interpreted as an ulcer crater. The stomach showed on microscopical examination a severe gastritis associated with the presence of a great many bacteria on the surface — a rather unusual finding in the stomach, since most stomachs are sufficiently acid so that organisms do not grow.

DR. ALFRED KRANES: Were you able to demonstrate varices?

DR. MALLORY: They were very marked and abundant, and I think they were the primary cause of hemorrhage, although the lesion in the stomach must have bled to some degree as well.

A PHYSICIAN: Was the spleen enlarged?

DR. MALLORY: Only slightly. He had bled enormous quantities. The spleen, at autopsy, following hematemesis, is frequently considerably smaller than it has been during life.

Microscopical examination of the liver showed something that I believe casts light upon the transient episode of jaundice five months before the terminal events. There were many small foci of fresh, infarct-like necrosis irregularly scattered throughout the organs. Usually, they were about 1 mm. in diameter and involved part or all of a small nodule of regenerated liver cells. This is not an infrequent finding in cirrhosis when severe hematemesis has preceded death by a number of hours. My explanation is that the blood supply in these scarred, irregularly reconstructed organs is no longer uniform. When hemorrhage from varices lowers the portal pressure and shock lowers the arterial pressure, ischemic damage occurs at susceptible points and liver function may be significantly depressed. It is not rare to see transient ascites develop following hematemesis, and jaundice, though less usual, would develop by the same mechanism and disappear when the liver circulation once again improved.

CASE 35372

PRESENTATION OF CASE

A two-day-old baby girl entered the emergency ward in an oxygenated incubator, with pronounced abdominal distention and vomiting.

This was the mother's first pregnancy and was without incident. Delivery, at an outside hospital, proceeded normally, prophylactic low forceps being used; breathing was spontaneous, and the cry was vigorous. The infant remained active and apparently well for the first twenty-four hours. On the second day of life, her color was described as "dusky," and she vomited dark, bloody fluid with her first feeding. Each subsequent feeding elicited vomiting. A small amount of meconium was said to have been passed by rectum on one occasion only. An enema produced only a small amount of meconium in addition to a 2-cm. plug of mucoid material. On the next morning she was considered normal by an examining pediatrician. Late that afternoon, "caput medusa" of the abdomen, distention and cyanosis were noted. The baby continued to vomit feedings and became progressively cyanotic and more distended. She entered this hospital fifty-six hours after birth.

Physical examination revealed a very ill infant, with cyanosis, which was more evident over the lower half of the body. Respiration was shallow and rapid; coarse, squeaky rales were present throughout both lung fields, more intense on the right. No cardiac murmur was noted. The abdomen was greatly distended without auscultable peristaltic sounds. No meconium was obtained on rectal examination. The anterior fontanel did not bulge.

The temperature was 98.2°F.

The white-cell count was 8200. The eosinophilic count was 0 per cent.

Radiograms in the supine position revealed marked upward displacement of both leaves of the diaphragm and compression of the lung fields by a distended abdomen. There was gaseous distention of the stomach and several loops of small bowel. In the right lower quadrant there was a C-shaped loop of dilated, gas-filled bowel, possibly small bowel, measuring 2.5 cm. in diameter. Throughout the abdomen there was a diffuse haziness indicative of intra-abdominal fluid.

A stomach tube was passed, and greenish substance obtained. A rectal tube was inserted. Infusions, chemotherapy and supportive measures were instituted.

Further radiograms in both the supine and upright positions revealed, in addition to the previous findings, a decompressed stomach and a large quantity of free gas and fluid in the peritoneal space (Fig. 1).

With continuous oxygen administration, abdominal paracentesis was done. One hundred and five cubic centimeters of dark brownish fluid with specks of yellowish-white material was obtained. Smears of this revealed copious gram-negative rods and gram-positive diplococci. Cyanosis increased. Respiration became irregular with periods of apnea. Artificial respiration was begun. Epinephrine, 0.5 cc., was given intracardially. Despite continued artificial respiration, cyanosis deepened, and the infant died five hours after admission.

Differential Diagnosis

Dr. Leo B. Burgin: In brief, we are faced with the problem of determining the cause of a series of events following one another rapidly in a two-day-old infant: persistent vomiting, abdominal distention, cyanosis, paralytic ileus, intra-abdominal fluid

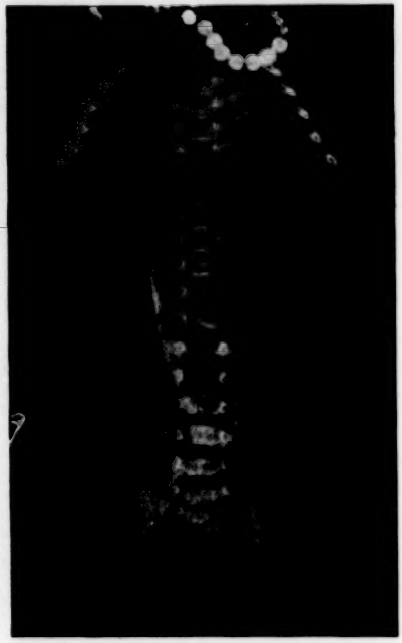

Figure 1.

and terminally gas and probably pus in the peritoneal space, with death at sixty-one hours.

A number of possibilities present themselves; in particular, congenital malformations of the gastrointestinal tract, meconium ileus and infection. Other possibilities may come to mind as the discussion proceeds.

Vomiting as a single episode or with occasional repetition is not uncommon in the normal newborn. The first episode described "dark bloody fluid." This may have had no further significance than that it represented aspiration of the blood at the time of delivery. There was no repetition of this. It was early for hemorrhagic disease of the newborn. Subsequently, the infant vomited at each feeding. We are not told the nature of the vomiting, whether it was projectile or merely regurgitation. Also, no description of the vomitus is offered. Later, "greenish" material was aspirated from the stomach, suggesting the presence of bile. An obstructive lesion under such circumstances would exist below the ampulla of Vater. Such an obstruction might be in the nature of atresia or stenosis, inspissated meconium or possibly malrotation of the cecum — the unrotated cecum lying across the lower end of the duodenum.

Vomiting is a frequent occurrence in infection. Although infection existed terminally as peritonitis, there was nothing to indicate its presence earlier. The white-cell count and temperature on admission were normal. Overwhelming infection or sepsis in the newborn may be present with a normal temperature and white-cell count. The eosinophilic count of 0 per cent merely indicates adrenal response or perhaps more accurately the "alarm-reaction" response to an overwhelming insult to the body. The absence of a bulging fontanel rules out intracranial vomiting, though not absolutely.

The rales in the chest might indicate pneumonia, but very likely some atelectasis and compression from a distended abdomen were largely responsible. One cannot rule out pneumonia.

The persistent vomiting was followed by abdominal distention, which appears to have been generalized. Obstruction in the region of the duodenum is apt to cause distention in the region of the epigastrium. Peristaltic waves are often visible. None were reported here.

It appears that in this case, the distention being generalized, any obstruction must have been lower down. This might rule out a malrotated cecum, which commonly lies across the third part of the duodenum. I might point out that in this anomaly the mesentery of the small bowel may lack the normal fixation, so that volvulus of the midgut, with gangrene and necrosis, may occur and might conceivably give the picture described. As we have indicated, distention caused by the unrotated cecum would be localized to the epigastrium — at least in the beginning. I assume that the generalized distention recorded here appeared almost at once. Also, the obstruction would not have been complete in the beginning, and we would have evidence of more stools or meconium to indicate patency of the gut.

The sudden appearance of a "caput medusa" suggests involvement of the portal vein, either from compression by distended gut or possibly from thrombophlebitis. The source of infection might be via the umbilicus, although the record says nothing about its appearance. It could look normal at this time and still be the source of infection.

Thrombophlebitis of the portal system can lead to gangrene of the bowel and subsequent rupture. I doubt whether such a process could take place in so short a time as the history indicates. Cyanosis, more evident in the lower extremities, suggests involvement possibly of the vena cava and iliac veins, most likely by compression. The absence of peristalsis suggests peritonitis and ileus.

Before going on to the x-ray studies, I believe we should say a word or two about the meconium. As one notes, very little was passed. The mucoid plug is a normal finding — often referred to as a "meconium plug." In the normal infant this is usually followed by the characteristic tarry, sticky meconium. After the plug was passed no further meconium was reported. Rectal examination failed to reveal any. This suggests obstruction from either atresia or inspissated meconium. A helpful test for atresia is the absence of cornified cells in the meconium. These cells from the vernix caseosa are desquamated into the amniotic fluid, which is swallowed by the fetus in utero. If no atresia exists, their presence can be detected in the meconium.

May we see the x-ray films?

Dr. Stanley M. Wyman: In the first film, which is of rather poor quality, the stomach is distended and the gas in the abdomen obscures the liver shadow, with a C-shaped loop of dilated bowel in the right lower quadrant. The diaphragm, as recorded, is displaced upward, and the lung fields are slightly compressed. A short time later, after the stomach had been aspirated, the gas in the stomach is decreased to normal, but the C-shaped loop of bowel in the left midabdomen remains. Again, gas is seen obscuring the shadows of the liver and spleen. This next film was taken at the same time in the upright position and shows a large quantity of gas with fluid in the abdomen. I do not see any evidence of gas in the colon.

Dr. Burgin: Have you any idea where the C-shaped loop would be?

Dr. Wyman: I should say that it was the ileum.

Dr. Burgin: The haziness reported in the first set of films as fluid need not indicate peritonitis. In infants, distention of the intestines alone may cause fluid to accumulate. Subsequently, there was evidence of rupture of a hollow viscus — obviously bowel — and the presence of the usual flora in the newborn: colon bacilli and, I presume, enterococci.

I believe the evidence points to intestinal obstruction due to an intrinsic lesion relatively low down in the bowel, which eventually resulted in rupture. The intestinal wall of the newborn is extremely thin, and rupture occurs relatively quickly if the distention is not relieved. I consider atresia the most likely cause of the lesion, although inspissated meconium — "meconium ileus" — remains an outside possibility.

In summary, early persistent vomiting, increasing generalized abdominal distention, absence of stools, accumulation of fluid and finally x-ray evidence of gas in the peritoneal cavity and distention of stomach and loops of bowel point to a diagnosis of atresia of the small bowel with rupture. On the basis of statistical frequency the atresia was most likely in the ileum. There should have been evidence of rupture, peritonitis, atelectasis and possibly some pneumonia.

Dr. F. Dennette Adams: In babies would there be distention enough to cause cyanosis?

Dr. Burgin: Certainly the newborn can become distressed following a meal causing difficulty in breathing. Mothers report that, after eating, a baby may have difficulty in breathing due to a distended stomach but not enough to produce cyanosis. I passed over the possibility of stenosis; there may be a patency of only 1 or 2 mm. in diameter, and for all practical purposes this may give signs and symptoms of obstruction.

Clinical Diagnoses

Congenital atresia of small bowel.
Peritonitis due to perforated viscus.

Dr. Burgin's Diagnoses

Congenital atresia of the bowel (ileum), with rupture.
Colon-bacillus peritonitis.
Pulmonary atelectasis.
Pneumonia?

Anatomical Diagnoses

Congenital defect of mesentery, with volvulus and perforation of ileum.
Peritonitis.
Pulmonary atelectasis, severe.

Pathological Discussion

Dr. Tracy B. Mallory: At autopsy when the abdomen was incised large amounts of hemorrhagic fluid exudate were found. The entire small bowel was dilated, the dilatation increasing as one progressed downward from the duodenum. The cause of this was discovered as the lower ileum was reached. A congenital defect was found in the mesentery through which a loop of ileum had protruded and then twisted on itself, forming a volvulus. Evidently at a later period three small perforations had developed in the gangrenous bowel of the volvulus.

Regarding the cyanosis, the astonishing thing at autopsy was that the child had breathed at all. The lungs were as totally atelectatic as those of a newborn baby who has never taken a breath. It was difficult to understand how the child could have lived long enough to develop such persistent and complete collapse.

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NEW VIRUS FROM DISEASES RESEMBLING POLIOMYELITIS

EARLY last summer Dalldorf and Sickles,[1] of the Division of Laboratories and Research of the New York State Department of Health in Albany, reported the isolation of a filtrable agent from the feces of 2 patients with muscular paralysis. These cases were observed during a small outbreak of poliomyelitis in upstate New York in August, 1947. The virus was distinct from that of poliomyelitis in that it could be isolated only by intracerebral inoculation of suckling mice or hamsters, but monkeys were not susceptible. The lesions produced consisted of widespread degeneration of the skeletal muscles, without any apparent lesions in the central nervous system or the large peripheral nerves.

The properties of this agent were different from those of any other known viruses. Furthermore, since it was recovered from patients with paralysis during a time when poliomyelitis was occurring to some extent in several areas of the country, it became a matter of considerable importance to learn more about its prevalence and its relation to clinical poliomyelitis. These workers, therefore, published their preliminary observations with the hope that other investigators would search for this agent and that some of them might perhaps have an opportunity to study the muscles in fatal cases of paralytic disease.

The first confirmation and extension of the findings of Dalldorf and Sickles has recently been published by Melnick, Shaw and Curnen,[2] of Yale University School of Medicine. The New Haven workers obtained a virus from the feces of 5 out of 13 patients with illnesses that resembled those of nonparalytic poliomyelitis or the so-called aseptic meningitis and from 2 additional patients with diagnoses of "fever of unknown origin." All their cases occurred in Connecticut and in Rhode Island during the summer and fall of 1948. They were also able to demonstrate neutralizing antibodies in the convalescent serums of all the 7 patients from whose feces the virus was isolated and in 5 additional patients with nonparalytic illness in whom attempts to isolate a virus were unsuccessful.

The properties of the virus obtained by the New Haven workers were the same as those of the agent isolated in Albany. The Yale workers were also able to demonstrate inapparent infection in chimpanzees after oral administration of the virus by recovering the virus from the nasopharynx and feces of these animals and also by proving the development of neutralizing antibodies for the new agent. In addition, one of the New Haven workers developed an accidental infection, which was characterized by fever of eight days' duration and a minimum of stiffness of the back, but no definite central-nervous-system symptoms. The new virus was recovered from the nasopharynx and feces of this worker, and neutralizing antibodies for the agent developed in his serum in increasing titer during convalescence.

Melnick and his associates extended their observations by a study of samples of feces that they had collected in previous outbreaks in different

parts of the country and had kept in a frozen state. They were unable to isolate the virus from two pools of feces, one obtained in New York in 1944 and the other in Los Angeles in 1948; both these pools yielded poliomyelitis virus on inoculation of monkeys. They did, however, recover both the new virus and the poliomyelitis virus from a pooled specimen of feces from 6 patients with nonparalytic poliomyelitis in Akron, Ohio, in 1947, and from another pooled specimen collected in Winston-Salem, North Carolina, in 1948. In addition, they were able to isolate the virus from the sewage of 6 cities in areas where the virus had been isolated from patients. Furthermore, the new agent was isolated from flies trapped in at least two of the same areas. A number of batches of flies collected during the epidemic of poliomyelitis that occurred in Texas in 1948 were also studied. Some of these yielded the new virus alone; others yielded only the poliomyelitis virus, and still others yielded both viruses.

The findings of the Yale workers indicate that the virus of Dalldorf and Sickles was widespread in this country in 1948 and possibly also in 1947. It is not yet entirely clear whether this is really a new virus that has made its first appearance as a human pathogen during recent years or whether it has been a factor in earlier outbreaks of paralytic infections in this country and elsewhere. The answer to this and to many other epidemiologic questions should be forthcoming as more of the stores of materials collected by these and many other workers on poliomyelitis are restudied. Further investigation should also indicate whether the epidemiology of the disease caused by the new virus is the same as that of poliomyelitis or whether it differs in such factors as seasonal distribution and the types of persons affected. The findings to date suggest that both viruses have similar epidemiologic features.

Although all the patients from whom the Yale workers isolated the strains of the new virus had nonparalytic cases, the original observations of Dalldorf and Sickles suggest that the disease caused by the new agent is not innocuous. Both their patients had definite muscular paralysis, and in one on them some of the paralysis was still present after seven months. It is also not yet clear how often this new virus will be discovered in clinical cases with paralysis. It is evident that the new virus has been found in areas and during periods in which paralytic poliomyelitis has been prevalent, but it remains to be seen how often it will be isolated in areas free of poliomyelitis and at times when this virus is not usually to be expected. The full clinical implications of these findings are therefore not yet evident. It is already apparent, however, that the diagnosis of poliomyelitis even during epidemics has now become further complicated in that infections with this new virus will have to be considered both in paralytic and in nonparalytic infections.

The spinal fluid in 9 out of 11 patients in whom infections with the new virus was demonstrated in New Haven showed a pleocytosis. The total number of leukocytes ranged from 27 to 600 per cubic millimeter, with 27 to 95 per cent mononuclear cells. There was a patient, however, from whom the virus was isolated and whose spinal fluid showed only 3 cells. Further correlations of both clinical and laboratory findings in patients with proved infections with this new agent and with the poliomyelitis virus are also needed to determine to what extent the two diseases, in both the paralytic and the nonparalytic forms, can be distinguished on the basis of simple clinical and laboratory findings. The recent observations indicate that, like the poliomyelitis virus, the new agent may produce fever without any specific meningeal or muscular symptoms. Infections with the new virus must therefore be included in the differential diagnosis of acute cases of "fever of unknown origin."

At the present time the demonstration of infections with the new virus of Dalldorf and Sickles is still a task for the few laboratories engaged in virus research. It is hoped that with further developments, less elaborate methods may be worked out that could be more readily applied in the usual hospital bacteriologic and serologic laboratories.

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"REVERENCE FOR LIFE"

AMERICA has entertained briefly on his first visit to its shores one of the world's foremost if hitherto little known physicians. Albert Schweitzer, now nearly seventy-five years of age, the son of an evangelical pastor of Alsace, has excelled in a half dozen of life's pursuits where it is given to most men to participate in only one or two.

A preacher, writer, teacher, philosopher and musician, the world's greatest interpreter of Bach Schweitzer, when the time came, turned his back, upon the exploitation of these accomplishments, renounced the material rewards of his genius and became a medical missionary in Equatorial Africa.

Schweitzer's character, so far as it is readily definable, is revealed in the titles of his works. *The Religious Philosophy of Kant* was published when he was 24, three years after he had determined that he would consider himself justified in living until he was 30 for science and art, "in order to devote myself from that time forward to the direct service of humanity." In 1903 he began *The Quest of the Historical Jesus*. His biography of Bach is the standard text on the life of that musician, but his autobiography, *Out of My Life and Thought* remains his best known work. *The Philosophy of Civilization* will be published this fall.

Like many who have attained their goal less completely, if no less humbly, Schweitzer came early to the conclusion that for him true happiness could be achieved only through a life of self-sacrificing service to others. To that goal he would channel his brilliant attainments, after he had brought them to maturity.

Still earlier he had adopted his own secret prayer to "protect and bless all things that have breath; guard them from all evil, and let them sleep in peace." He tells later in his autobiography, as quoted by Sperry* in these pages, how the definition of this belief finally came to him.

Journeying up the river toward his hospital he was searching in his mind for some basic ethical principle, but fruitlessly. And then:

> Late on the third day at the very moment we were making our way through a herd of hippopotamuses, there flashed upon my mind, unforeseen and unsought, the phrase "Reverence for life." For all life.

This was the essence of the belief that had moved him, at 21, to continue his brilliant career in music and in preaching for only ten years more and then to study medicine and give his life wholly to others. It was the credo that brought the ultimate happiness of contentment to his mind, previously troubled despite his intellectual achievements and material success; the abnegation that always must motivate the priest or the missionary whether in foreign fields or in areas of service nearer home.

This same reverence for life and willingness for sacrifice in its behalf provide the basic material in the character of the true physician wherever his course may lie.

It is of little moment whether Schweitzer's decision was partly intellectual or wholly emotional or whether the services that he has performed in darkest Africa, comparable to those of Grenfell in Labrador, might have reaped a more productive harvest in some more fruitful area. All life, according to his uncompromising standards, must be reverenced and consequently preserved and strengthened and upheld.

*Sperry, W. L. Moral problems in practice of medicine. *New Eng. J. Med.* 239:985-990, 1948.

DEMON RUM

THE fact that the uncertainties of life in a complex world lend added attraction to the offerings of the neighborhood package store accounts largely for man's eager resort to alcoholic beverages. In peaceful times as well as in disturbed ones, however, in simple as in complicated surroundings, thinking man, so far the supreme product of nature's biologic efforts, still finds it necessary to bypass with the help of alcohol the results of his ability to reason.

Some persons are able to use alcohol in this way to a limited degree and remain in general control of their activities; others — and the number is increasing — become slaves to the habit that they have acquired. Whatever the original cause of their addiction and whether or not it still persists, the addiction has with them become in itself a disease that requires treatment.

The two articles by Thimann, published a week ago and in the present issue of the *Journal*, discuss

in particular the conditioned-reflex treatment of chronic alcohol addiction as it is carried out at the Washingtonian Hospital in Boston.

The conditioned-reflex treatment, at present the most promising form of therapy for alcoholism, was first reported in England in 1930. Apomorphine was the drug used in these early experiences, and an estimated success of 35 per cent was attained. In this country the Shadel Sanitarium in Seattle, Washington, first reported nearly a decade ago a considerable number of patients treated with the conditioned reflex. A 7.8 per cent solution of emetine was used, and 64.3 per cent total abstinence was claimed as a result. A further report from this institution was published a year ago in the *Journal*.[1]

At the Washingtonian Hospital, where the conditioned reflex was instituted seven years ago, a slightly modified technic has been adopted, supplemented by "methodic psychotherapy and part-time hospitalization and manipulation of the patient's environment."

Emetine is a drug not without its disadvantages, as is indicated by Thimann and has been pointed out by Kattwinkel[2] in his report of a case treated with emetine, with a fatal outcome. It lowers the blood pressure and in excessive doses causes arrest of the heart in diastole. The nausea induced by it may be accompanied by diarrhea, and it may be followed by muscular pain and weakness.

In its effects on the cardiovascular system lie the chief objections to emetine, Thimann reporting that 5 of the 282 patients in his series had cardiovascular manifestations, with 2 deaths. The death reported in detail occurred in a patient who flagrantly disregarded instructions.

The precautions that should be taken to prevent untoward reactions are listed by Thimann and have been referred to editorially in these columns.[3] If due consideration is given to them, emetine may be employed with safety, although the search for a less toxic substitute continues.

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BOSTON'S CHEST X-RAY PROGRAM

Boston, following the precedent established by various other large cities of the country, is about to launch an intensive chest x-ray program. The campaign will start on September 21 and continue until January 14; its goal is to obtain a chest x-ray examination, if possible, of every person of fifteen years of age or over who lives, works or transacts business in the city.

The younger age group is excluded from the program because of its much lower incidence of tuberculosis and because of other screening methods that are more effective than mass x-ray study — such as tuberculin testing, and case finding as a result of the adult program.

The program will be conducted under the auspices of the Boston Health Foundation, Incorporated, an organization made up of the vital health and welfare agencies of the city, which have united at this time for this specific purpose. A far-reaching system of committees has been devised, each with its particular area of responsibility. Not the least important among them is the medical committee, under the chairmanship of Dr. Dwight O'Hara, which is further divided into subcommittees for the interpretation of the program to physicians, for the supervision of and the proper referral of positive cases, and for the review of those cases that require it.

Suitable personnel and twenty mobile x-ray units are being loaned by the United States Public Health Service for the program, and these will operate, area by area, in twenty health districts established as such for the occasion. Persons with normal chest x-ray films will be promptly notified of the fact by mail; those showing any suspicion of active tuberculosis, cardiovascular disease or other pathologic conditions will be referred to their physicians, and their physicians will be so notified.

Boston, with a tuberculosis death rate in 1948 of 56.1 per 100,000 population labors under the distinction of a rate nearly twice that of the country as a whole. The program that is about to start will be of great value in correcting this situation. Of the greatest value in furthering the enterprise will be the co-operation of the medical profession in the best New England tradition of service.

Perseverance is a prominent element in western character. It is infused into the institutions of learning as well as in river navigation. The medical department of the University of St. Louis is strongly organized, and the system of medical education in it is creditable to Missouri. . . .

Boston M. & S. J., *September 12, 1849*

MASSACHUSETTS MEDICAL SOCIETY

The fall meeting of the Council of the Society will be held at 10:30 a.m., October 5, at the Boston Medical Library.

H. QUIMBY GALLUPE, M.D.
Secretary

DEATHS

BERNHARDT — Henry M. Bernhardt, M.D., of Arlington, died on August 31. He was in his forty-first year.

Dr. Bernhardt received his degree from Boston University School of Medicine in 1935. He was physician for the Massachusetts Institute of Technology and Phillips Academy, Andover, and was a member of the New England Ophthalmological Society.

His widow, a son, a brother and a sister survive.

SCUDDER — Charles L. Scudder, M.D., of Brookline, died on August 19. He was in his ninetieth year.

Dr. Scudder received his degree from Harvard Medical School in 1888. He was a consulting surgeon at the Massachusetts General Hospital and was a fellow of the American College of Surgeons and the American Surgical Association and a member of the Society of Clinical Surgery and the New England Surgical Society.

A son and a daughter survive.

WASHBURN — Frederic A. Washburn, M.D., of Boston, died on August 20. He was in his eighty-first year.

Dr. Washburn received his degree from Harvard Medical School in 1896. He was formerly superintendent of the Massachusetts General Hospital and founded the Baker Memorial Hospital. He was director of the Massachusetts Eye and Ear Infirmary from 1915 to 1934 and was appointed commissioner of institutions in Massachusetts in 1934. He was a fellow of the American Medical Association.

His widow survives.

WILDER — Ella A. Wilder, M.D., of Middletown, Connecticut, died on July 20. She was in her fifty-third year.

Dr. Wilder received her degree from Boston University School of Medicine in 1923. She was a member of the New England Obstetrical and Gynecological Society and a fellow of the American Medical Association.

Her mother survives.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

LABORATORIES APPROVED FOR DIAGNOSTIC SEROLOGY

Since the completion of the tests for 1948–49, the following laboratories have been granted approval. Only laboratories approved by the Department of Public Health for *diagnostic* serology may legally make the premarital and prenatal blood tests required by law. This is in addition to the Wassermann Laboratory of the Department, which is evaluated annually by the Public Health Service.

LOCATION	LABORATORY
Boston	Boston Dispensary
	Boston Health Department
	Commonwealth Clinical Laboratory
	Leary Laboratory
	Massachusetts Memorial Hospitals
Brockton	Brockton Health Department
Brookline	Sias Laboratories
Clinton	Clinton Hospital
Fall River	Union Hospital
Great Barrington	Fairview Hospital
Haverhill	Hale Hospital
Holyoke	Holyoke Hospital
	Providence Hospital
Lowell	Lowell General Hospital
Montague City	Farren Memorial Hospital
New Bedford	Burt Clinical Laboratory
	St. Luke's Hospital
Newton	Newton-Wellesley Hospital
Pittsfield	Pittsfield General Hospital
	St. Luke's Hospital
Quincy	Quincy City Hospital
Salem	Salem Hospital
Springfield	Mercy Hospital
Tewksbury	State Infirmary
Westfield	Noble Hospital
Worcester	Worcester City Hospital
	Worcester Health Department
	St. Vincent Hospital

CORRESPONDENCE

INCURABLE READER

To the Editor: Noticing the review of Dr. Ronchese's book on *Occupational Marks and Other Physical Signs*, I was reminded of our old friend Dr. Maurice Richardson. He was constantly urging us to *observe*. I remember one day he was questioning an unknown patient and asked, "Are you a steam or gas fitter?" Astonishment showed on the man's face as it did on the faces of the students. Dr. Richardson smiled and pointed to a faint tattooed scar on the man's nose, shaped like a new moon.

I think this is the fifty-fifth or fifty-sixth continuous year that I have had the *Journal* and perused it with pleasure and profit — an outstanding journal.

PHILIP C. MEANS, M.D.

Chula Vista, California

SEMANTICS

To the Editor: I have just read your editorial "Essentially Useless" in the July 14 issue of the *Journal*, in which you rightfully call attention to "uncritical use of the language." I should like to point out the consistent use of the word "regime" in indicating in your journal a program of therapy. I have also noted in another of your editorials ("Medical Practice in Great Britain" in the *Journal* of February 3) the use of "regimen" as a system of government. The following definitions are given in my *Funk and Wagnalls Desk Dictionary*:

Regime, n. System of government or administration; social system.

Regimen, n. 1. A systematized course of living, as to food, clothing, etc. 2. Government; control.

It seems from the above that "regimen" applies either to government or to therapy, but that "regime" should be limited to use in referring to government.

HERBERT N. JACOBS, M.D.

San Francisco

Note: *Webster's International Dictionary* (1948) is less scrupulous in the definition of regime: 1. Mode or system of rule or management; character of government or of the social system. 2. *Hydraulic*. . . . 3. *Med*. Regimen. — ED.

ACROMIOCLAVICULAR DISLOCATION

To the Editor: A perusal of Dr. Boardman Marsh Bosworth's paper, "Complete Acromioclavicular Dislocation," which appeared in the August 11 issue of the *Journal*, prompts the following observations.

Complete dislocation at the acromioclavicular joint is not invariably associated with avulsion of the coronoid and trapezoid ligaments, or as Dr. Bosworth calls them, the "coracoclavicular ligament." This statement is based on the work of Poirier and Rieffel, in their study entitled "Mécanisme des luxations sus-acromiales de la clavicule: leur traitement par la suture asscuse" (*Arch. gén. de méd.* **1**: 396-422, 1891), and of Cadanat, in his article "The Treatment of Dislocations and Fractures of the Outer End of the Clavicle" (*Internat. Clin.* **27**:145-169, 1917). It has recently been confirmed by Urist in a paper entitled "Complete Dislocation of the Acromioclavicular Joint" (*J. Bone & Joint Surg.* **28**:813-837, 1946). I was associated with Dr. Urist during a part of the time he was carrying out his studies on this subject and can confirm his conclusions. On the basis of numerous dissections of fresh material and observations at the operating table, Urist states: "When these structures (the joint capsule and attachments of the trapezius and deltoid muscles) were severed, to simulate the tearing or stretching which occurs in them with dislocation, complete dislocation of the outer end of the clavicle was possible without injury to the conoid or trapezoid ligaments. It is true that rupture of the conoid and trapezoid ligaments allowed greater displacement of the clavicle, but the picture was altered quantitatively, not essentially."

Integrity of the clavicle or its associated joints is not essential for normal function of the shoulder. Fitchet, in an exhaustive study entitled "Cleidocranial Dysostosis: Hereditary and familial" (*J. Bone & Joint Surg.* **11**:838-866, 1929), found almost no evidence of impairment of function in his cases or those reported in the literature. Although it is true that in the presence of injury to the clavicle or dislocation of the acromioclavicular joint the shoulder "droops" downward and forward, there is also an upward component of force that has not generally been recognized. Gordon, in 1875, called attention to this in his book, *A Treatise on the Fractures of the Lower End of the Radius, on Fractures of the Clavicle, and on Reduction of the Recent Inward Dislocations of the Shoulder Joint* (London: J. & A. Churchill), and pointed out that in the absence of the strut of the clavicle the muscles of the shoulder girdle as a whole tend to force the shoulder toward the apex of the truncated cone of the thorax.

Complete dislocation of the acromioclavicular joint is not incompatible with excellent function. I recently had an opportunity of examining a professional football player, who is able to throw forward passes with great skill despite the fact that the distal end of his clavicle lies on the superior surface of his acromion even at rest. Two similar cases in college athletes have been seen in the past two years.

Motion between the clavicle and the coracoid process of the scapula is considerable and complex. This can easily be demonstrated by a simple experiment, which was repeated today and in which a healthy, twenty-eight-year-old man, who had never suffered an injury to his shoulder girdle, was placed upright facing an x-ray cassette and films were taken with the arm hanging at the side and held directly overhead. Between the former and the latter the coracoid process moved 1 inch toward the distal end of the clavicle and rotated upward an estimated 40°, and the clavicle itself rotated on its own axis upward and backward an estimated 90°.

Fixation or "suspension" between the coracoid process and the clavicle such as Dr. Bosworth advocates severely must strain either the fixation apparatus or the bones involved. The effect of the fixation seems to be the same as fusion of the acromioclavicular joint, which Dr. Bosworth very properly condemns. Even if care is taken to leave the proximal end of the screw loose, as Dr. Bosworth recommends, limitation of motion between the coracoid and the clavicle must be marked.

A plea for conservative management of acromioclavicular joint injuries was made by Thorndike and Quigley in a paper "Injuries to the Acromioclavicular Joint: A plea for conservative treatment" (*Am. J. Surg.* **55**:250-261, 1942). The results of treatment of 138 acromioclavicular dislocations or separations of varying degree in athletes were reported. In none was operation found necessary. As Urist pointed out, associated injury to the trapezius and deltoid muscles plays a large part in separation of the distal end of the clavicle from the acromion after an injury to the shoulder. As the integrity and tone of these injured muscles return, an apparently severe separation often changes to a trivial laxity of the joint that produces neither symptoms nor disability.

Surgery, when necessary, is usually indicated for cosmetic reasons, or for relief of pain, which may accompany the imperfect function of chronic partial dislocation. In either case simple removal of the outer end of the clavicle, as recommended by Gurd, in his report entitled "Surplus Parts of the Skeleton" (*Am. J. Surg.* **74**:705-720, 1947), has been satisfactory. For the rare patient whose livelihood depends on prompt restoration of appearance and function, a lashing operation, using strips of fascia lata, may be indicated.

T. B. Quigley, M.D.

Boston, Massachusetts

Dr. Quigley's letter was submitted to Dr. Bosworth, who offers the following reply:

To the Editor: I was delighted to read Dr. Quigley's comments on my recent paper and feel complimented that he was inspired to make them. Thank you for granting me the opportunity to reply.

It may be that complete dislocation can occur without tearing of the coracoclavicular ligaments. I have not seen this happen.

I believe that whether or not integrity of the acromioclavicular joint is essential for normal function is a matter of opinion and depends upon one's definition of "normal."

I admit that complete acromioclavicular dislocation may not be incompatible with excellent function, but, if it occurs, it must be the exception rather than the rule.

Dr. Quigley is correct in stating that motion between the clavicle and the coracoid process is complex. Whether or not it is "considerable" again depends upon definition of that word.

Dr. Quigley writes that of 138 acromioclavicular dislocations reported by him in 1942 none required operation. I congratulate him! However, he does not indicate how many of these were complete dislocations. This is the very crux of the problem, since treatment and prognosis will vary according to whether the joint separation is *partial* or *complete*. Any discussion of the subject that fails clearly to distinguish between the two merely confuses the reader. May I point out that the paper in question was expressly limited to *complete* dislocations.

Whether or not the insertion of a screw in the manner I describe is called "fixation" or "suspension" is beside the point. It works.

Boardman Marsh Bosworth, M.D.

Bronxville, New York

A QUESTION OF CONSISTENCY

To the Editor: I am somewhat confused by an apparent basic inconsistency between your interesting editorial on the Danish program for criminal psychopaths in the July 7 issue of the *Journal* and your fine editorial comment in the July 14 issue concerning Dr. Alexander's sobering revelations of medical atrocities under Hitler.

The former editorial endorses the policy of the Danish program and refers with apparent approval to castration as a condition of release of sex offenders, "just as numbers of the inmates of mental-deficiency institutions have been sterilized before release."

On the other hand, the July 14 editorial wholly endorses Dr. Alexander's position, a major tenet of which is the fact that medical practices of exactly this sort may lead to that situation in which criteria for sterilization reflect political as well as medical motivations.

It is difficult for me to reconcile the Danish position with the warnings expressed by Dr. Alexander. I should appreciate the comments of the editors on the points raised in the two editorials cited.

I take this opportunity, in passing, of commending the *Journal* for its continued policy of fairness and open-mindedness, which has made it one of the few medical organs that

have maintained objectivity in the sociologic as well as the scientific aspects of medicine.

E. RICHARD WEINERMAN, M.D.
Visiting Associate Professor of Medical Economics
University of California School of Public Health
Berkeley, California

Note: The Herstedvester editorial referred to by Dr. Weinerman committed the *Journal* to the extent of saying that the penal code of Denmark had much to recommend it. The editors did not thereby intend to commit themselves to either approval or disapproval of the particular point that Dr. Weinerman has stressed — that of castration as a condition of release of sex offenders.

The address by Dean Sperry published in the *Journal* for December 23, 1948, is recalled, in which he states that often the choice between the right course and the wrong one is not between black and white but between two shades of gray, both of which have points that recommend them. — ED.

BOOK REVIEWS

Textbook for Almoners. By Dorothy Manchée, almoner, St. Mary's Hospital, London. With a foreword by Sir Alfred B. Howitt, C.V.O., M.D., president, Institute of Almoners. 8°, cloth, 466 pp., with 49 diagrams and drawings. Baltimore: Williams and Wilkins Company, 1947. $7.50.

In ancient times an almoner was the keeper of the purse, although at St. Bartholomew's Hospital in London the "Almoners," later called the House Committee, originally had the duty of interviewing all patients and admitting them to the hospital at discretion. Today the almoners in England are the medical social workers, as they are known in the United States. Sir Charles Loch, the secretary of the Family Welfare Association, formerly the Charity Organization Society, was the founder of the modern almoning profession. As early as 1885 he became interested in social work in hospitals, and in 1894 he succeeded in interesting his organization in the matter; in 1895 Miss Mary Stewart, a secretary of the Charity Organization Society, was appointed to the position of almoner at the Royal Free Hospital, the first almoner to be appointed in England. Her duties as laid down by the hospital board were to prevent any abuse of the hospital by persons able to pay for medical treatment, and to refer destitute patients to the proper authorities. It is only within recent years that hospitals in the United States have taken steps to control this abuse. The movement has steadily progressed until today in England there is a well established profession of almoning with its governing institute, composed of management and labor, broadly speaking, and its own hospital-almoners' association. In October, 1945 the *Interim Report of the Social and Preventive Medicine Committee of the Royal College of Physicians* was published. It confines the functions of the almoners to medical social work. The Institute stated that the chief function of an almoner shall be medicosocial work in its various aspects. They may assume as required certain administrative responsibilities, such as checking patients' ability to pay fees.

This book constitutes a valuable document concerning the development of medical social work in England. The text is divided into four parts: origin and growth of the almoner service; social legislation; financial assistance; and social aspects of disease. In the last part are discussed the various subdivisions of the practice of medicine.

The text was printed in Great Britain and is well done with a good type on a light, soft non-glare paper. Although the book is dated 1947, it was not distributed until recently in the United States. Miss Manchée is the author of two previous small books: *Social Service in a General Hospital* and *Social Service in the Clinic for Venereal Disease.* Although the text is based on London experience and on British legislation and regulations, the book should be in all collections on social service work, both medical and general.

Medicine throughout Antiquity. By Benjamin L. Gordon, M.D. With a foreword by Dr. Max Neuburger. 8°, cloth, 818 pp., with 157 illustrations. Philadelphia: F. A. Davis Company, 1949. $6.00.

Dr. Gordon has traced the history of early medicine from the beginning of man, reputed to be about half a million years B.C., to the end of the Greco-Roman period, terminating with the fall of Rome in 476 A.D. He has compiled from all available widely recognized sources the facts pertinent to his subject. The work has been divided into two main parts: the prehistoric and protohistoric periods; and the Greco-Roman period. This last period is susceptible to a fuller exposition because of the extensive literature on it. The first period, the prehistoric, begins with the first appearance of man and ends when history began to be recorded; here one must depend on archeology, paleology and paleopathology for facts revealed by human fossils, cave and stone drawings and paintings, and on primitive instruments. In the protohistoric period the facts are drawn from such documents as the code of Hammurabi, the Old Testament of the Bible and the works of Homer; this period extended until the rise of the Ionian school of philosophy about 600 B.C. The second period begins with Thales of Miletus, of the Grecian school of philosophers. In the first division of his work the author includes material on paleology and evolution; on the primitive concepts of disease and death, and on the early concepts of nature; and on the Ionian and Athenian schools of philosophy as necessary for an understanding of early medicine. In the chapter on early man one notices the omission of Osborn's great work, *Men of the Old Stone Age.* Likewise, the outstanding work of Hovorka and Kronfeld, *Volkmedicin*, seems to have been missed. After the general chapters the medicine of the various races is discussed, beginning with the Assyrians and Babylonians and including the ancient Egyptians, Hebrew medicine, Persians, Hindus, Japanese and the prehistoric American Indians. The last two chapters of the book are on Talmudic medicine, and they would better have been placed with the one on Hebrew medicine. Many persons confuse the meaning of the words Hebrew and Jew. Modern scholars limit the word Hebrew to the language and refer to the race as the Jews. There is a looseness in dating Jewish medicine. In the opening paragraphs on ancient "Hebrew medicine" the time of Abraham is noted in one place as 2000 B.C. and in another as 2500 B.C. Likewise, the period of the Talmud is not dated. The second section of the work is divided into two parts on Grecian and Roman medicine, beginning with chapters on Aesculapian and Homeric medicine, on the influence of philosophy on medicine and on the Ionian and Eleatic schools of philosophy, and on the medical philosophers and practitioners. The whole subject is covered from Hippocrates to the empirics. The part on Roman medicine considers the period from the Methodic school to Galen. The vivid description by Ovid of the pestilence that raged in Rome during the period of his life, 43 B.C. to 17 A.D., is given in an English translation. It is noted that the famous description by Thucydides of the plague at Athens is not mentioned. There are a number of typographic errors in the text, such as "Calumella" for "Columella" and "Gellius" for "Aulus Gellius." The various chapters are documented with lists of references and notes to passages in the text. The references in many cases are poorly cited, omitting edition place and date and, in some cases, the title. There is a long index, but it does not contain all the names in the text or references. The type, printing and illustrations are excellent, but the coated paper makes the volume too heavy for continuous reading. The material on Jewish medicine is valuable because it is in English and easier to use than the monumental work of Preuss, *Biblisch-talmudische Medizin.* The history should be in all medical libraries and medical-history collections.

Hindu Medicine. By Henry R. Zimmer, Ph.D. Edited with a foreword and preface by Ludwig Edelstein, Ph.D. 12°, cloth, 203 pp. Baltimore: Johns Hopkins Press, 1948.

The late Professor Zimmer, in 1940, delivered the seventh course of the Hideyo Noguchi lectures at Johns Hopkins Institute of the History of Medicine. He was preparing the material for publication, after making considerable revision, enlargement and rearrangement, when he died suddenly early in 1943. He had completed the first lecture and the greater part of the second lecture, but the third lecture was represented by a great deal of fragmentary memoranda. It was quite evident from a study of the material that the work, as originally planned, could not be published. Professor Edelstein and Mrs. Zimmer considered the matter and finally decided to print the first two lectures from the manuscript without alteration. The third lecture represents a reconstruction, as far as possible, of the author's ideas and concepts of

certain diseases and cures and two appendixes, comprising the translation of the tables of contents of the *Susruta-Samhita* and the *Encyclopedia of the Elephant Man*. This reconstruction, which was made by Dr. Edelstein, is contained in a long preface of fifty-six pages. Professor Zimmer had no idea of competing with Jolly's scholarly work on Indian medicine, contained in the *Encyclopedia of Indo-Aryan Research*, Vol. 3, Strassburg, 1901. He was endeavoring to interpret Hindu culture so as to understand its meaning in its own terms, and to ascertain its value for men today. The two lectures printed are entitled "Medical Tradition and the Hindu Physician" and "The Human Body: Its forces and resources." The text is concluded with notes to the introduction and the lectures, and an index of passages from the classical Hindu texts. The small volume is well published but lacks an index to the contents. It should be in all medical-history collections.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Biological Reactions Caused by Electric Currents and by X-Rays: A theoretical study of the phenomena of excitation in the nerve by different electric currents and of the biological reactions caused by X-Rays, both based upon a common principle. By J. Th. van der Werff, M.D., D.Sc. 8°, cloth, 203 pp., with 38 illustrations. New York: Elsevier Publishing Company, Incorporated, 1948. $5.00.

This monograph is a highly technical presentation of its subject, written for physiologists and radiologists. Although the study is biologic, the author has made an extensive use of mathematics. However, two of the highly technical parts are concluded with chapters entitled "Summary" and "Conclusions," in which all the mathematics, except the fundamental equations, have been left out. The text is divided into three parts: the first consists of a general introduction and essentials (including a hypothetical equation of metabolism). In this part the author points out that the phenomena of excitation caused by electric currents, especially those of excitation of the nerve, and the biologic reactions caused by x-rays are analogous to such an extent that it is highly probable that they may be explained from a common principle. Likewise, in this part, the author has tried to formulate this principle but has had to resort to higher mathematics, without which the formulation could not have been made. The second part discusses the electric excitation of the nerve and the third, biologic relations caused by x and gamma rays. The pertinent literature is referred to throughout the text and instead of a regular bibliography, there is a list of the authors mentioned and the sources of their articles. There are also author and subject indexes. The book is well published in every way. The comparatively high price for such a small volume is justified by the great number of intricate mathematical formulas. The volume should be in all collections on radiology and physiology.

Diseases of the Ear, Nose, and Throat. By Douglas G. Carruthers, M.B., Ch.M. (Sydney), consulting ear, nose and throat surgeon, Canterbury District Memorial Hospital, Sydney. Second edition. 8°, cloth, 344 pp., with 140 illustrations. Baltimore: Williams and Wilkins Company, 1948. $7.00.

The first edition of this small textbook for students and general practitioners was published in Sydney in 1943. This second edition has been revised and the use of penicillin and the sulfonamides has been included, as well as the newest form of treatment for tropical otitis externa. The technic for tonsillectomy is given in detail. There is a "pharmaceutical" index, comprising standard recipes, and also an index of subjects. The text was printed in Great Britain and is well done. The publication on the whole is excellent.

Reprints from the Oxford-Loose-Leaf Medicine. By Walter C. Alvarez and others. 8°, paper. New York: Oxford University Press, Incorporated, 1948. Not for sale.

This collection of reprints comprises twenty-one articles taken from the latest edition of the *Oxford System of Medicine*. They cover the whole field of medicine and are supplied only to subscribers to the complete work and are not for sale. They are valuable to libraries because they offer in a single form various worthwhile articles that may be lent, and the bound volumes of the system may thus be kept available for reference.

Veterans Administration Technical Bulletin, Vol. I, 1946 and 1947; 4°, cloth, 240 pp. Washington, 1948. Vol. II, 1948; 4°, cloth, 168 pp. Washington, 1949.

These two volumes for 1946–1948 contain thirty-six articles of a clinical character covering the whole field of practical medicine. They are intended primarily for the staff of the Veterans Administration. They are produced in an excellent manner by offset printing and are substantially and well bound. They should be in all reference medical libraries.

Surgery of the Hand. By Sterling Bunnell, M.D., consultant in hand surgery to the Surgeon General, and licentiate of American Board of General Surgery and Plastic Surgery. First edition. 4°, cloth, 930 pp., with 779 illustrations. Philadelphia: J. B. Lippincott Company, 1948. $16.00.

This second edition of a standard special work has been revised to bring its contents up to date since the publication of the first edition in 1944. Considerable material has been added, mostly to the chapters on reconstruction, injuries, infection and tumors. Lists of references are appended to the various chapters. The book is profusely and well illustrated. There is a good index. The volume is recommended for all medical libraries, and it should prove valuable to surgeons interested in the hand.

Cardiology. By William Evans, M.D., D.Sc., F.R.C.P., physician to the cardiac department of the London Hospital, physician to outpatients of the National Heart Hospital and consulting cardiologist to the Royal Navy. 8°, cloth, 330 pp., with 269 illustrations and 15 tables. New York: Paul B. Hoeber, Incorporated, 1948. $7.50.

This condensed treatise is intended for the medical student who desires a concise book to prepare him for his final examinations. The work is based on a series of lectures given to postgraduate students at the London Hospital. The material is well organized. The text was printed in Great Britain with a good type. There is considerable waste of paper in the make-up of the index. It is surprising how many British books are being imported in pages into the United States and then bound and distributed by various publishers, in preference to promotion of works by native authors. Of course, this practice is helping Great Britain in its export program.

Cancer of the Esophagus and Gastric Cardia. Edited by George T. Pack, M.D., clinical professor of surgery, New York Medical College, and attending surgeon, Memorial Hospital for Cancer and Allied Diseases. 8°, cloth, 192 pp., with illustrations. St. Louis: C. V. Mosby Company, 1949. $5.00.

This monograph is a reprint of a symposium originally published in *Surgery* for June, 1948. Eighteen specialists presented eleven articles, three of which discuss the transthoracic and transdiaphragmatic methods. The publishing is excellent. The book should prove valuable to surgeons interested in the subject, and libraries could well substitute it for the bound volume of the periodical.

Shock: And allied forms of failure of the circulation. By H. A. Davis, M.D., C.M., associate professor of surgery and director, Division of Surgery, Graduate School of Medicine, College of Medical Evangelists, Los Angeles Division, senior attending surgeon, Los Angeles County General Hospital and White Memorial Hospital, and visiting surgeon, Cedars of Lebanon Hospital and California Hospital. 8°, cloth, 595 pp., with 55 illustrations. New York: Grune and Stratton, 1949. $12.00.

This comprehensive monograph considers shock in all its varying aspects. Beginning with a historical introduction, including classification, the text proceeds from physiology,

biochemistry, diagnosis and pathology, through the various types of shock, and ends with treatment. The large literature on the subject is reviewed throughout the text. Long bibliographies are appended to the various chapters. There is a good index. The type, printing and illustrations are excellent. The volume is very heavy for its size, owing to the use of a hard filled paper, probably justified by the number of reproductions of microscopical slides. The book is recommended for all medical libraries and should prove valuable to surgeons and other persons interested in shock.

The Basis of Chemotherapy. By Thomas S. Work, Ph.D., research staff, National Institute for Medical Research, London; and Elizabeth Work, Ph.D., research staff, Department of Chemical Pathology, University College Hospital Medical School, London. 8°, cloth, 435 pp., with 42 illustrations and 38 tables. New York: Interscience Publishers, Incorporated, 1948. $6.50.

Here is another British book, imported in sheets and bound and distributed in the United States, but it is a good book and merits serious consideration. The authors have attempted to weld many diverse sciences into a single pattern in order to find a basis for chemotherapy. They have used the resources of organic and physical chemistry, biochemistry, bacteriology, pharmacology and therapeutics, and have analyzed and reviewed the pertinent and current literature in all these fields. The bibliography appended to the text comprises fifty-four pages. After a historical introduction, the chapters deal with cell metabolism, essential metabolites, enzyme inhibition, drug antagonism and resistance, and the relation of structure and activity of drugs. There is a good index, and the book is well printed. It should be in all reference collections in medical and scientific libraries.

The Business Side of Medical Practice. By Theodore Wiprud, executive director and secretary, Medical Society of The District of Columbia, and managing editor, *Medical Annals of the District of Columbia.* Second edition. 12°, cloth, 232 pp., with 23 illustrations. Philadelphia: W. B. Saunders Company, 1949. $3.50.

The first edition of this manual was published in 1937. This edition has been revised in part, and some of the text has been entirely rewritten and other portions expanded. New chapters on opportunities for medical leadership, group medical practice and the future of the doctor have been included in the second edition. A competent lawyer reviewed the material on the legal aspects of medical practice. There is a good index, and the book is well published. This important volume should be in all medical libraries and in the offices of all physicians.

Ghosts of the Air-Waves. By Antonio L. Tauro. 12°, cloth, 165 pp. Boston: Meador Publishing Company, 1949. $2.00.

This novel deals with the problem of unlawful abortion.

Mayo Clinic Diet Manual. By the Committee on Dietetics of the Mayo Clinic. 8°, paper, 329 pp. Philadelphia: W. B. Saunders Company, 1949. $4.00.

This manual outlines the general and special dietary procedures used in the Mayo Clinic and Mayo Foundation and the hospitals of Rochester, Minnesota, represented on the Mayo Clinic committee. In addition to the various diets an appendix contains a number of tables on foods and their special contents and on their composition, standard diabetic diets for children and for adults and height-weight-age tables for men and women. Originally, the material was mimeographed, but in this third edition it has been printed and made available to dietitians outside Rochester. A detailed table of contents takes the place of an index.

NOTICES

ANNOUNCEMENTS

Dr. Jacob B. Burke announces the opening of an office at 162 Shurtleff Street, Chelsea, for the practice of obstetrics and gynecology.

Dr. Max G. Carter announces the opening of an office at 442 Temple Street, New Haven, Connecticut, for the practice of thoracic and cardiovascular surgery.

MASSACHUSETTS CHAPTER OF AMERICAN ACADEMY OF GENERAL PRACTICE

The fall clinical meeting of the Massachusetts Chapter of the American Academy of General Practice will be held in Boston on Wednesday, October 19. The morning will be spent at clinics at the Massachusetts General Hospital, with a luncheon, afternoon papers and banquet at the Hotel Puritan.

More complete details will be furnished later.

MASSACHUSETTS PSYCHIATRIC SOCIETY

The annual meeting of the Massachusetts Psychiatric Society will be held at the Hotel Sheraton, Boston, on Friday, October 28, at 7:00 p.m. The speaker will be Carl A. L. Binger, M.D., of New York City, assistant professor of clinical psychiatry at Cornell University Medical College, and formerly United States representative to the International Congress at London in 1948.

This is a dinner meeting, and reservations will be accepted from members of the medical and allied professions.

NEW ENGLAND PEDIATRIC SOCIETY

A meeting of the New England Pediatric Society will be held in Boston on Wednesday, September 28.

PROGRAM

11:00 a.m.–1:00 p.m. Presentation of cases illustrating research in therapy of disseminated cancer. Dr. Sidney Farber and staff. Amphitheater, Peter Bent Brigham Hospital.
2:30–4:30 p.m. Clinical sessions conducted by Dr. Allan M. Butler and associates. Amphitheater of Building C, Harvard Medical School.
5:30 p.m. Refreshments. Longwood Towers.
6:30 p.m. Dinner. Longwood Towers (charge, $3.25).
7:30 p.m. Advances in the Therapy of Infectious Diseases with the Newer Antibiotics. Dr. Emanuel B. Schoenbach, associate professor of preventive medicine and assistant professor of medicine, Johns Hopkins University School of Medicine, and physician, Johns Hopkins Hospital.

TUBERCULOSIS REHABILITATION SOCIETY

The fall meeting of the Tuberculosis Rehabilitation Society will be held at the Cedarcrest Sanatorium, Newington, Connecticut, on Friday, October 14.

The Society was organized in the spring of 1949 with a membership covering the entire New England area. Its object is the promotion of tuberculosis rehabilitation, with special reference to the exchange of technical information, the promotion of interagency and interstate relations, development of standards for procedures and personnel in this work and promotion of publicity of tuberculosis rehabilitation.

UROLOGY AWARD

The American Urological Association offers an annual award of $1000 (first prize of $500, second prize $300 and third prize $200) for essays on the result of some clinical or laboratory research in urology. Competition is limited to urologists who have been in such specific practice for not more than five years and to residents in urology in recognized hospitals. The first-prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Hotel Statler, Washington, D. C., May 29 to June 1, 1950.

Full particulars may be obtained from the secretary, Dr. Charles H. de T. Shivers, Boardwalk National Arcade Building, Atlantic City, New Jersey. Essays must be in his hands before February 20, 1950.

(*Notices concluded on page xv*)